

UNITED STATES  
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

87TH MEETING

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Thursday

January 28, 1999

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The Meeting took place in the Natcher Building, Main Auditorium of the National Institute of Health, 45 Center Drive, Bethesda, Maryland at 9:00 a.m., Chairman Robert Califf, presiding.

MEMBERS PRESENT:

- DR. ROBERT CALIFF, Acting Chairman
- JOAN C. STANDAERT, Executive Secretary
- DR. RAYMOND LIPICKY
- DR. CINDY M. GRINES
- DR. JOANN LINDENFELD
- DR. UDHO THADANI
- DR. MARVIN KONSTAM

CONSUMER REPRESENTATIVES:

- DR. THOMAS GRABOYS
- DR. ILEANA PIÑA

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A-G-E-N-D-A

Public Comments: 4  
Conflict of Interest announcement: 7

Pfizer Presentation

- Dr. Steven Ryder 11
- Dr. Jeremy Ruskin 13
- Dr. Craig Brater 32
- Dr. Tillman Friedrich 130
- Dr. Craig Pratt 153
- Dr. Jeremy Ruskin 178

Committee Discussions and Recommendations 198

1 P-R-O-C-E-E-D-I-N-G-S

2 (9:00 a.m.)

3 ACTING CHAIRMAN CALIFF: I'm Rob Califf,  
4 and I will be the Acting Chairperson today. We would  
5 like to start by asking if there is anyone who would  
6 like to give public comment.

7 Yes? Come forward and please use a  
8 microphone and identify yourself again.

9 MR. SASICH: My name is Larry Sasich, and  
10 I'm from Public Citizen Research Group in Washington,  
11 D.C.

12 Public Citizen had requested, on January  
13 7th, through the Freedom of Information Act, access to  
14 the FDA and other data sent to your Advisory Committee  
15 concerning the safety and efficacy of Dofetilide.

16 Our request was denied, and we were deeply  
17 concerned about the evidence that this drug can cause  
18 potentially life-threatening heart rhythm  
19 disturbances, even though it may be approved to treat  
20 or prevent heart rhythm abnormalities.

21 Despite not being allowed access to this  
22 data, and the fact that peer review in medical

1 literature is not an adequate substitute for the FDA  
2 reviews of safety and efficacy, we do have serious  
3 concerns based on a brief review of the published  
4 literature about the safety of this drug, because of  
5 its proarrhythmic effects in association with Torsade.

6 We are also apprehensive about the use of  
7 an antiarrhythmic drug to prevent the recurrence of an  
8 arrhythmia, after the increased risk of death was found  
9 with a class 1C antiarrhythmic drugs, and the cardiac  
10 arrhythmia suppression trial in the early 1990s.

11 Several studies in patients with atrial  
12 fibrillation or flutter of normal volunteers, have led  
13 to our concerns over the potential of this drug to  
14 cause arrhythmias.

15 In the study of IV Dofetilide in 16  
16 patients with recent onset atrial fibrillation, 2 of  
17 15 patients, or 13 percent completing the study,  
18 suffered episodes of Torsade.

19 In a study of 10 healthy male volunteers  
20 given oral Dofetilide, one subject exhibited  
21 asymptomatic polymorphic ventricular tachycardia.  
22 When its corrected QT interval was excessively

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1 prolonged.

2 The authors felt that this may have been  
3 due to a repolarization abnormality unmasked by the  
4 drug. These authors caution that the efficacy of drug  
5 for terminating an arrhythmia is not necessarily  
6 equivalent to efficacy in preventing recurrence. And  
7 we would add that it may not be as safe, either.

8 They also pointed out that Dofetilide  
9 manifests electrophysiologic features that may  
10 predispose to apparent ventricular conduction during  
11 atrial fibrillation that may be difficult to  
12 distinguish from short runs of ventricular  
13 tachycardia.

14 Public Citizen is on record as being  
15 deeply troubled about drugs that have been approved by  
16 the FDA with known safety problems that were  
17 subsequently withdrawn from the market after many  
18 deaths and injuries.

19 The three most recent examples are dexfen  
20 Fluramine, Mibefradil, which three members of this  
21 Advisory Committee thought should not have been  
22 approved, and Bromfenex.

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1 We are concerned that this trend is  
2 continuing with the recent approval of Cilostazol for  
3 the treatment of intermittent claudication, a painful  
4 but non-life threatening condition that is most  
5 effectively managed by a program of structured  
6 exercise, and the possible approval of this drug,  
7 Dofetilide.

8 We urge that this committee decide that  
9 Dofetilide, a drug that can cause potentially life  
10 threatening arrhythmia should not be approved to  
11 prevent recurrent arrhythmias because, if approved,  
12 the tragic experience of the class 1C antiarrhythmic  
13 drugs will be relived.

14 Thank you very much for the opportunity  
15 and your attention.

16 ACTING CHAIRMAN CALIFF: Are there any  
17 other public comments?

18 (No response.)

19 ACTING CHAIRMAN CALIFF: Hearing none we  
20 will now proceed with our agenda. Joan, do you have  
21 announcements?

22 SECRETARY STANDAERT: Yes. This will be

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1 the conflict of interest statement for January 28th,  
2 1999.

3 The following announcement addresses the  
4 issue of conflict of interest with regard to this  
5 meeting, and is made a part of the record to preclude  
6 even the appearance of such at this meeting.

7 Based on the submitted agenda for the  
8 meeting, and all financial interests reported by  
9 Committee participants, it has been determined that  
10 all interest in firms regulated by the Center for Drug  
11 Evaluation and Research present no potential for an  
12 appearance of a conflict of interest at this meeting  
13 with the following exceptions.

14 In accordance with 18USC208 B3, full  
15 waivers have been granted to Dr. Marvin Konstam, Dr.  
16 Ralph D'Agostino, and Dr. Peter Kowey. A copy of  
17 these waiver statements may be obtained from the  
18 Agency's Freedom of Information office, room 12-A30 of  
19 the Parklawn Building.

20 In addition, Drs. Dan Roden, Milton  
21 Packer, and Lemuel Moyer are recused from participating  
22 in all matters related to Tikosyn.

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1 Further, we would like to disclose that  
2 Dr. Califf's institution was previously involved in  
3 research relating to Tikosyn, and we believe this  
4 should be disclosed.

5 FDA believes that it is important to  
6 acknowledge our participant's involvement so that his  
7 participation can be objectively evaluated. Dr.  
8 Califf's employer, the Duke Clinical Research  
9 Institute previously participated in two studies of  
10 Tikosyn.

11 Dr. Califf's only involvement in these  
12 trials was to ensure that the projects were being  
13 effectively conducted, and the results were  
14 disseminated in an academic form. He was not  
15 personally involved in any way in the conduct of these  
16 trials.

17 With respect to FDA's invited guest  
18 speaker, Dr. Arthur Atkinson, he has reported  
19 interests which we believe should be made public, to  
20 allow the participants to objectively evaluate his  
21 comments.

22 Dr. Atkinson has reported that he owns



1 stock in Pfizer, and Pharmacia, and Upjohn. In  
2 addition he is a former corporate officer of the  
3 Upjohn company that developed one of the competing  
4 products to Tikosyn.

5 In the even that the discussions involve  
6 any other products or firms not already on the agenda,  
7 for which an FDA participant has a financial interest,  
8 the participants are aware of the need to exclude  
9 themselves from such involvement, and their exclusion  
10 will be noted for the record.

11 With respect to all other participants, we  
12 ask in the interest of fairness that they address any  
13 current or previous financial involvement with any  
14 firm whose products they may wish to comment upon.

15 That concludes the statement for today.

16 ACTING CHAIRMAN CALIFF: Thank you. We  
17 have a large amount of data to review today, and we  
18 have a number of guests. Just looking at the  
19 logistics of the room, it is going to be very hard for  
20 many of us to see the slides, unless we sit down  
21 front.

22 And for that reason and others, just for

1 the Committee, I would like to at least put forth a  
2 proposition that we very much limit the discussion  
3 until the presentation is complete, unless there are  
4 major issues of clarification of the data that is  
5 presented.

6 With that, Committee members who need to  
7 see the slides and can't, we will move down front, and  
8 we invite the sponsor now to come forward with the  
9 presentation.

10 DR. RYDER: Good morning, my name is  
11 Steven Ryder, I'm Senior Vice President of Clinical  
12 Research, U.S. Clinical Research for Pfizer Central  
13 Research.

14 Dr. Califf, Dr. Lipicky, members of the  
15 Cardiorenal Advisory Committee, ladies and gentlemen,  
16 on behalf of Pfizer I want to thank you for this  
17 opportunity to present the data on Tikosyn, which  
18 supported safety and effectiveness in the conversion  
19 to, and maintenance of sinus rhythm in patients with  
20 chronic atrial fibrillation.

21 In the time allowed for this presentation  
22 we will present the results of both clinical and

1 relevant non-clinical studies of Tikosyn more commonly  
2 known by its generic name, Dofetilide.

3 The clinical development program for  
4 Dofetilide was extensive, and has allowed Pfizer to  
5 characterize the potential clinical benefits and risks  
6 of Dofetilide to a degree that is uncommon for this  
7 class of drug.

8 The overall results of this program have  
9 led to the conclusion that the antiarrhythmic  
10 properties of Dofetilide have therapeutic benefit in  
11 patients with chronic atrial fibrillation.

12 We will present the results of two placebo  
13 controlled clinical trials that show that Dofetilide  
14 is effective in maintaining normal sinus rhythm after  
15 either pharmacologic, or electrocardial version from  
16 atrial fib.

17 The results of the same two placebo  
18 controlled trials, as well as other trials in  
19 supraventricular arrhythmias, and results from two  
20 large mortality trials in patients with significant  
21 structural heart disease show that individualization  
22 of the starting dose reduces the incidence of Torsade

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1 de points to an amount equal to, or less, than that of  
2 approved agents.

3 The results of the two large mortality  
4 trials do not suggest an increase in mortality among  
5 patients taking oral Dofetilide. In addition we will  
6 show data that there are no significant non-cardiac  
7 risks associated with Dofetilide treatment.

8 This is the agenda for our presentation.  
9 Our presentation will begin and end with discussions  
10 of the current therapeutic environment for treating  
11 chronic atrial fib, and the potential utility of  
12 Dofetilide in this setting. These will be presented  
13 by Dr. Jeremy Ruskin.

14 Three presentations of Dofetilide clinical  
15 data will be given. One on its  
16 pharmacokinetic/pharmacodynamic properties by Dr.  
17 Craig Brater, one in clinical efficacy by Dr. Tilman  
18 Friedrich, and one on clinical safety by Dr. Craig  
19 Pratt.

20 With that I would like to begin the  
21 sponsor presentation by introducing Dr. Jeremy Ruskin.

22 DR. RUSKIN: Thank you, Dr. Ryder. Dr.

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1 Califf, Dr. Lipicky, members of the committee, ladies  
2 and gentlemen.

3 I would like to begin by just offering  
4 some very brief comments as an overview with regard to  
5 the problem of atrial fibrillation. I will try to  
6 keep my comments very brief.

7 I will offer just a few words about the  
8 epidemiology and the clinical consequences of atrial  
9 fibrillation, and then say a few words about the  
10 current options available for the treatment of this  
11 very common clinical problem.

12 Atrial fibrillation is the most common  
13 arrhythmia requiring therapy that the clinician faces.  
14 It is also, unfortunately, the least well understood  
15 from an electrophysiologic standpoint, and the most  
16 difficult to treat.

17 In addition, at the present time, our  
18 therapeutic options for the management of this problem  
19 are relatively limited.

20 Atrial fibrillation is a very common  
21 problem affecting more than two million patients in  
22 the United States alone. And while it is not terribly

1 uncommon in younger patients, it is far more prevalent  
2 in the older population, with six percent of people  
3 over the age of 65 having atrial fibrillation.

4 This slide is a composite slide showing  
5 you two different population age distributions. In  
6 pink is the age distribution of the U.S. population,  
7 and in blue bars is the distribution, or age  
8 distribution of patients with atrial fibrillation.

9 And the point that I wish to make from  
10 this slide is a simple one, and that is that as this  
11 baby boom becomes the senior boom, the absolute  
12 numbers of patients with atrial fibrillation is going  
13 to increase very significantly, and this is, at least  
14 to the best of my knowledge, the only arrhythmia that  
15 we currently treat that is increasing substantially in  
16 numbers.

17 Atrial fibrillation also consumes a great  
18 deal of hospital time, and it generates enormous cost.  
19 This slide summarizes for you the number of hospital  
20 days in thousands per year, consumed by various  
21 arrhythmia diagnoses, and as you can see atrial  
22 fibrillation swamps all other arrhythmias, consuming

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1 about a million hospital days per year, at a cost of  
2 approximately a billion dollars.

3 And this refers only to atrial  
4 fibrillation as a primary diagnosis. Its contribution  
5 as a secondary diagnosis to prolong length of hospital  
6 stay and other situations, is also well appreciated.

7 The consequences of atrial fibrillation  
8 are also well known. The primary reason for treating  
9 the problem relates to symptoms. Perhaps less well  
10 appreciated is the very important contribution of  
11 atrial fibrillation to the development of congestive  
12 heart failure.

13 The problems of increased risk for stroke  
14 and death are also very widely and well appreciated.  
15 And, unfortunately, in 1999 we have no data for any  
16 form of antiarrhythmic therapy that control of atrial  
17 fibrillation reduces risk for stroke or death. Those  
18 data are simply not available.

19 It is also important to emphasize that  
20 patients with atrial fibrillation represent a broad  
21 spectrum with regard to symptoms, ranging from those  
22 who are entirely unaware of the presence of their

1 arrythmia, to those who are incapacitated by it.

2 And, obviously, any discussion of therapy  
3 directed at rhythm control must be involved with, and  
4 directed towards patients with significant symptoms.

5 This cartoon simply delineates for you  
6 differences between paroxysmal and chronic atrial  
7 fibrillation, and this distinction is important in  
8 light of what you will hear with regard to the data on  
9 Dofetilide.

10 Paroxysmal atrial fibrillation, which has  
11 been the commonest target of drugs which have been  
12 submitted for approval for an AF indication, have been  
13 studied largely in patients with frequently recurring,  
14 highly symptomatic discrete episodes of AF, in which  
15 symptoms of palpitations, dizziness, and dyspnea  
16 predominate.

17 And, generally, in patients in whom the  
18 onset and the offset of the event, both in terms of  
19 the rhythm, and the symptoms accompanying it, are very  
20 discrete and well-defined.

21 On the other hand, chronic atrial  
22 fibrillation which generally affects a somewhat sicker

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1 population, more commonly is associated with dyspnea,  
2 fatigue, and weakness, and diminished effort  
3 tolerance. And it is often a lot more subtle and  
4 insidious, in terms of its onset, and a lot more  
5 difficult to measure precisely because of the  
6 chronicity of the problem, and its frequent  
7 association with other forms of heart disease.

8 This slide summarizes for you the  
9 available treatment options for the management of  
10 atrial fibrillation, and these are well appreciated by  
11 everybody here, and include the use of rate control in  
12 patients in whom loss of atrial transport is not the  
13 primary problem, but rapid rates are.

14 In the subset of patients, however, in  
15 whom loss of atrial transport is the primary cause of  
16 symptoms, antiarrhythmic drugs are used for  
17 maintenance of sinus rhythm, and the available options  
18 are listed here, and include the Class 1A and 1C  
19 drugs, the 1C being widely employed but limited by  
20 labeling to patients without structural heart disease,  
21 precisely because of the results of the cardiac  
22 arrhythmia suppression trial, which you heard mentioned

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1 in the public comment period.

2 Sotalol and Amiodarone, which are not  
3 approved for use in atrial fibrillation factor widely  
4 employed for this problem in patients with structural  
5 heart disease, and constitute important therapeutic  
6 options in this population.

7 Nonpharmacologic therapies are in their  
8 infancy at this point, and at present, and at least  
9 for the foreseeable future, applicable only to a very  
10 small percentage of patients with symptomatic atrial  
11 fibrillation.

12 I show this slide simply to emphasize one  
13 point, and that is that in 1999 we have  
14 nonpharmacologic treatment options in the form of  
15 curative catheter ablation techniques for every  
16 arrhythmia listed on this slide, with the exception of  
17 atrial fibrillation, for which the mainstay of therapy  
18 remains drug therapy.

19 This slide lists for you the various  
20 agents currently approved for the treatment of atrial  
21 fibrillation, for conversion of atrial fibrillation to  
22 sinus rhythm, Ibutilide, and Quinidine are both

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1 currently labeled for that indication. Ibutilide, as  
2 you know, available only for parietal use.

3 In terms of prevention of recurrent  
4 paroxysmal atrial fibrillation in patients without  
5 structural heart disease, the two available agents  
6 include Flecainide and propranol.

7 In terms of prevention of relapses of  
8 atrial fibrillation, the only approved agent is  
9 Quinidine.

10 This slide summarizes for you the total  
11 prescriptions written in 1997 for antiarrhythmic  
12 agents, and the vast majority of these are written for  
13 atrial fibrillation, as you will see on the following  
14 slide.

15 The only point that I want to make is that  
16 at the present time the two most widely employed  
17 agents are Quinidine and Amiodarone. Quinidine is  
18 still the most commonly prescribed drug for this  
19 problem. Amiodarone, the most widely used agent for  
20 atrial fibrillation in the setting of advanced  
21 structural heart disease, in particular congestive  
22 heart failure.

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1                   And this simply confirms the fact that the  
2 vast majority of these prescriptions are written for  
3 supraventricular indications, that is for atrial  
4 fibrillation. What this slide illustrates for each of  
5 the antiarrhythmic agents in blue is the percentage of  
6 prescriptions written for supraventricular  
7 indications, compared to other indications.

8                   In conclusion atrial fibrillation is a  
9 problem of enormous public health significance. It  
10 affects a large number of patients, and is associated  
11 with very significant morbidity and costs to the  
12 health care systems.

13                   Finally, at the present time our current  
14 therapeutic options for maintenance of sinus rhythm in  
15 highly symptomatic patients, particularly those with  
16 structural heart disease, are very limited.

17                   Thank you.

18                   ACTING CHAIRMAN CALIFF: Before you sit  
19 down, I think the order we would like to go in, if  
20 there are questions, would be to start with Dr. Grines  
21 and Dr. Kowey, who are the primary reviewers, and then  
22 come back to the others.

1 DR. ATKINSON: Jeremy, I just have a  
2 question for you, which is going to play into some  
3 things that come on later, but we still use drugs a  
4 lot for atrial flutter, even though I agree with you  
5 that ablation is a very realistic option for many of  
6 those patients.

7 Do you believe that drugs of this class,  
8 that we are going to talk about today, should be  
9 expected to have a differential effect on flutter  
10 versus atrial fibrillation in their efficacy?

11 And that plays in, obviously, to a risk  
12 benefit assessment, which you are going to come into  
13 later.

14 DR. RUSKIN: Well, I think that there are  
15 theoretical reasons why they might work better for  
16 flutter than fib, and you are as aware as I am of the  
17 reasons, since most flutter is a macro re-entrant  
18 right atrial rhythm, one would expect drugs that  
19 prolong action potential duration, and alter  
20 wavelength, would have a favorable effect on re-  
21 entrant rhythms, particularly macro -re-entrant  
22 rhythms.

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1           So I would expect a differential efficacy  
2           there, with a dominant effect on flutter, or a more  
3           prominent effect on flutter.

4           That said, certainly, and I can only speak  
5           for where I work, our approach to flutter, when it is  
6           pure flutter, is largely an ablative approach at the  
7           present time. I suspect that is true of you, as well.

8           ACTING CHAIRMAN CALIFF: Other questions?  
9           Dr. Grines?

10          DR. GRINES: I have a question about the  
11          annual utilization of hospital beds, and I was just  
12          wondering if you knew the breakdown of patients who  
13          are just newly diagnosed with atrial fibrillation,  
14          that is why they were admitted, versus one with  
15          recurrent episodes?

16          DR. RUSKIN: Yes, it is a very important  
17          question, and I'm sorry, I don't have that data, and  
18          it was not available in the source that that slide was  
19          derived from, I just don't know.

20          ACTING CHAIRMAN CALIFF: We can start in  
21          this end with Dr. Thadani.

22          DR. THADANI: Regarding Amiodarone use, I

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1 know it is not approved, but at least in my  
2 institution is used very often. And the fact one  
3 feels safe or even in a patient with pulmonary valve  
4 dysfunction.

5 So what do you -- you are using it in your  
6 institution for, say, 100 or 200 milligrams? I  
7 realize there are pulmonary toxicity of that, but it  
8 is a fairly safe drug, and realizing it is not  
9 approved for maintenance. So that is one question.

10 Other question is I'm not sure, in chronic  
11 AF, I realize the symptoms are subtle, a lot of  
12 patients don't have symptoms, and that will probably  
13 come up in the discussion, and NIH is, as you know, is  
14 doing a study to say the rate control is as good as  
15 controlling sinus rhythm. So how much emphasis you  
16 really want to pay just on conversion?

17 I realize some of the patients don't like  
18 Afib, so if you could address those two issues?

19 DR. RUSKIN: With regard to your first  
20 question the answer is yes, I certainly use  
21 Amiodarone, and I'm very glad I have it as an option.  
22 It is, in fact, the only option that I think we have

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1 in patients with advanced heart disease, particularly  
2 congestive heart failure, and AF that requires therapy  
3 for maintenance of sinus rhythm. So it is a very  
4 effective drug, and we certainly use it.

5 It is not completely free of risk, as you  
6 know, particularly with regard to long term organ  
7 toxicity. But it is a very important agent, and in  
8 Europe it is the treatment of first choice, in many  
9 countries, for atrial fibrillation.

10 Unfortunately, at the present time, in the  
11 very sick group it is the only option that we have.

12 With regard to the question of whether or  
13 not to treat chronic atrial fibrillation I think is a  
14 very difficult one, but it has to come back to the  
15 question of symptoms. At least in my own practice I  
16 would only initiate a path of treatment and  
17 conversion, and long term suppression in situations  
18 where there are significant symptoms associated with  
19 the loss of atrial transport.

20 And I would not want to suggest, in any  
21 way, that the patient with chronic atrial fibrillation  
22 who is functioning at a high level, and not

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1 symptomatic from the AF itself, should be treated with  
2 antiarrhythmic drug therapy.

3 DR. THADANI: So you are saying they  
4 should not be?

5 DR. RUSKIN: If they are asymptomatic for  
6 the AF, they certainly, in my personal opinion they  
7 certainly should not be treated.

8 DR. THADANI: So the rate control, and  
9 anticoagulation is pretty reasonable way to do it?

10 DR. RUSKIN: Yes, I think it is in that  
11 subset.

12 DR. TEMPLE: Would you agree that is a  
13 matter of opinion at this point, as Udho said, there  
14 is a randomized trial addressing that right now?

15 DR. RUSKIN: Absolutely. I think that  
16 everything we are talking about with regard to  
17 precisely when to treat is largely a question of  
18 personal opinion, and one has to make judgements about  
19 the level of symptoms that the patients present with.  
20 It is a clinical judgement.

21 In terms of data on outcome, as you've  
22 said, there is a large scale multicenter trial that

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1 will, hopefully, provide some information about  
2 whether there is a mortality benefit to maintenance of  
3 sinus rhythm, compared to rate control, but we simply  
4 don't know that at the present time.

5 ACTING CHAIRMAN CALIFF: Dr. Temple, and  
6 then Dr. Cohn.

7 DR. TEMPLE: When you referred to  
8 symptoms, which ones do you think are most  
9 troublesome, and also respond to placement into sinus  
10 rhythm?

11 DR. RUSKIN: That is a critical question.  
12 What I'm offering now is just personal perspective as  
13 somebody who practices medicine, so I don't have data  
14 to support this, this is just a question of  
15 experience, and I would be interested in other  
16 people's thoughts.

17 But in the subset with long term atrial  
18 fibrillation, meaning months to longer than that, what  
19 I see most commonly is diminished effort tolerance,  
20 and exertional dyspnea with minimal activity.

21 And there are people with chronic atrial  
22 fibrillation who know that their lives are infinitely

1 in sinus rhythm than in AF. They may not be acutely,  
2 absolutely incapacitated by the AF, but they feel that  
3 they are very different people in terms of their  
4 ability to function and exert themselves in sinus,  
5 compared to atrial fibrillation.

6 DR. TEMPLE: Just one other question.  
7 When someone is converted would you, ordinarily, or  
8 would everybody ordinarily stop any anticoagulants, or  
9 do you keep that on just in case they recur?

10 DR. RUSKIN: I think that one of the  
11 highest risk periods for systemic embolism is  
12 immediately after conversion. So I think that most  
13 people would accept the need to be very aggressive  
14 about anticoagulation following cardioversion, in  
15 virtually everybody who can take an anticoagulant.

16 DR. TEMPLE: And is there some time after  
17 conversion when you breathe a sigh of relief and stop  
18 it?

19 DR. RUSKIN: The conventional wisdom, Dr.  
20 Temple, is that you can stop it if there is no  
21 recurrence at a month or so. I don't do that unless  
22 I'm absolutely sure. And there are many, many

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1 situations where I feel I can't be sure, and I'm very  
2 aggressive about continuing anticoagulation in a large  
3 percentage of patients.

4 DR. TEMPLE: So you would not urge that  
5 one of the obvious benefits of prolonging the period  
6 of time before you recur, or anything like that, is  
7 that you get spared coumadin?

8 DR. RUSKIN: I generally don't -- I don't  
9 argue that point. There are some patients in whom the  
10 onset of AF is so clearly defined by symptoms that you  
11 can be quite confident that if they are not having  
12 symptoms that you can stop anticoagulation.

13 But that, by no means, applies to  
14 everybody.

15 ACTING CHAIRMAN CALIFF: Peter? You had  
16 another question.

17 DR. KOWEY: Jeremy, can I just clarify a  
18 little bit of a nosology, because it is going to  
19 happen all through the day. And I know that people  
20 have tried to put names on atrial fibrillation but I'm  
21 really kind of concerned about this term chronic.

22 Maybe we can agree that maybe John Camm is

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1 right, maybe there is a persistent form of AF, which  
2 I think is the target for the clinical trials we are  
3 going to talk about today, and chronic is maybe atrial  
4 fibrillation that is fixed, and with no hope of  
5 reversion.

6 Do you think that is reasonable?

7 DR. RUSKIN: I think that is entirely  
8 reasonable, and your assessment of what we are talking  
9 about is accurate. I think we are talking about, in  
10 the Camm classification, what would be persistent  
11 atrial fibrillation, rather than permanent atrial  
12 fibrillation; persistent being longstanding, but  
13 convertible.

14 ACTING CHAIRMAN CALIFF: If we could try  
15 to keep discussion to pertinent things to the  
16 application, and not just interesting issues in atrial  
17 fibrillation. Udho?

18 DR. THADANI: Another question relevant,  
19 perhaps, to the discussion later on. When I was  
20 reading this, they say Afib has to persist for 24  
21 hours, or whatever. That is something new to me. To  
22 me Afib recurs, it recurs, you know? You

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1 cardioversion somebody, and two hours later the  
2 patient is in Afib, you cardioversional therapy didn't  
3 work.

4 And the definition in the two trials, let  
5 me hear it, I'm not prematurely emptying it, is one is  
6 one hour, one is 24 hours. To me, a patient goes into  
7 Afib, is that a risk of thromboembolic, so I'm going  
8 to anticoagulate him for a while.

9 What is your feeling on the review, when  
10 you are talking about maintenance, because a lot of  
11 patients, even what we call as a sustained afib, after  
12 cardioversion could be paroxysma. And that is why  
13 your rate at six months could be different at 12  
14 months.

15 So just a short comment on that.

16 DR. RUSKIN: Yes, I agree with what you  
17 are saying. There are protocol issues around  
18 definitions of recurrence that you will hear about,  
19 and that I'm sure will be discussed.

20 ACTING CHAIRMAN CALIFF: Any questions on  
21 the right-hand side? Joan?

22 SECRETARY STANDAERT: Just a quick

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1 question. You said the median age of people in the  
2 United States with atrial fibrillation is 75, and I  
3 assume that about half are women, is that correct?

4 DR. RUSKIN: Yes, it is roughly evenly  
5 distributed, although because there are more women  
6 alive -- excuse me, it is not evenly distributed. It  
7 is more common in males than females.

8 But because there are more women alive  
9 over the age of 65 it is roughly equally balanced in  
10 the population.

11 ACTING CHAIRMAN CALIFF: Okay, I think we  
12 are doing pretty well, let's move on to the next  
13 presentation.

14 DR. RUSKIN: Thank you. I would like to  
15 introduce Dr. Craig Brater who will discuss clinical  
16 pharmacology of Dofetilide.

17 DR. BRATER: Thank you, Jeremy. Dr.  
18 Califf, Dr. Lipicky, members of the Advisory  
19 Committee, ladies and gentlemen.

20 I'm Craig Brater, I'm from Indiana  
21 University, and I have been asked to present the  
22 clinical pharmacology aspects of this drug.

1           With all drugs it is important to  
2 understand the relationship between dose and response,  
3 as shown here. And this is particularly the case with  
4 cardiovascular drugs.

5           The sponsor has conducted an extensive  
6 clinical pharmacology program on Dofetilide in order  
7 to understand the relationship shown here, and the  
8 determinants of disposition and response.

9           In defining this relationship one must  
10 understand the variables shown here on the bottom that  
11 can permute the linkage between dose and  
12 concentration, and then between concentration and  
13 response.

14           In this presentation I will first  
15 summarize studies that examine the determinants of  
16 pharmacokinetics, and then pharmacodynamics.

17           In so doing I will show the derivation of  
18 a method for individualizing dosing that accounts,  
19 firstly, for pharmacokinetic variability, and secondly  
20 for pharmacodynamic variability, and then I will  
21 conclude with data showing the PK/PD relationship with  
22 Dofetilide to serve as a background for further

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1 discussions of efficacy and safety.

2 Let's first turn our attention to the  
3 pharmacokinetic characteristics of Dofetilide. The  
4 absolute bioavailability is greater than 90 percent.  
5 As such there is no risk for drug interactions  
6 involving pre-systemic clearance.

7 And, moreover, this high bioavailability  
8 implies negligible metabolism at the gut wall by  
9 CYP3A4, and negligible intestinal secretion by P-  
10 glycoprotein.

11 There is no effect of food on  
12 bioavailability, although as one would predict, T-max,  
13 the time at which peak concentrations occur, was  
14 delayed by about one hour.

15 In pondering absorption one must also  
16 consider interactions of bioavailability that can  
17 decrease absorption. The lack of effect of the drugs  
18 listed here indicates limited risk therein.

19 There was an interaction of absorption  
20 with immediate release for Verapamil, which caused a  
21 43 percent increase in peak Dofetilide concentration  
22 that was due to more rapid absorption. There was not

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1 an equivalent increase in overall exposure.

2 This may be due to increased GI blood flow  
3 that has been reported to occur with Verapamil,  
4 whether or not this occurs with sustained release for  
5 Verapamil, or with potassium is unknown.

6 The majority of Dofetilide dose,  
7 approximately 70 percent, is eliminated by the kidney.  
8 The magnitude of Dofetilide renal elimination  
9 indicates that Dofetilide clearance is predictably  
10 affected by level of renal function, which also  
11 indicates a need for dosage adjustment based on renal  
12 function.

13 In a moment I will show you data assessing  
14 the relationship of Dofetilide clearance to renal  
15 function, and how it allows design of a regiment for  
16 dosage modification.

17 Dofetilide has a high renal clearance that  
18 exceeds GFR, approximately 250 milliliters per minute.  
19 Secretion is the dominant component of renal  
20 elimination, accounting for 85 percent of renal  
21 excretion.

22 This high degree of renal secretion

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1 indicates a need to define the relevant secretory  
2 pathway, and thereby identify potential drug  
3 interactions that might occur therein. I will also  
4 discuss this issue subsequently.

5 The next slide shows the relationship  
6 between renal function, estimated by the Cocockroft-  
7 Gault equation, and Dofetilide clearance. On the X  
8 axis is creatinine clearance, estimated from the  
9 Cocockroft-Gault equation, on the wax, this is  
10 Dofetilide systemic clearance.

11 This relationship has been assessed as  
12 individual studies in patients with moderate and  
13 severe renal impairment in patients throughout phase  
14 2 and 3, and in a renal substudy of the Diamond  
15 studies.

16 The slope of this relationship is  
17 consistent across all groups, and is approximately  
18 0.2. The very high R squared value of 0.84, and  
19 consistent slope, indicate that the majority of  
20 variability in Dofetilide disposition can be accounted  
21 for by renal function, thereby allowing prospective  
22 dose adjustment.

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1                   These findings have also been confirmed in  
2           the    patient    population    studies,    or    patient  
3           pharmacokinetic    studies    of    over    1,400    patients.  
4           Subsequently I will show you the method for dose  
5           adjustment, and how it performs.

6                   But before that let's address the question  
7           of renal secretion. There are three pathways by which  
8           the kidney secretes drugs. One is the organic  
9           cationian pathway, the organic cation pathway, or via  
10          P-glycoprotein.

11                   The organic cation pathway is not a  
12          reasonable consideration because Dofetilide is  
13          positive charged at physiological PH, in fact it has  
14          three PKs, all of which are basic.

15                   In terms of them sorting out whether or  
16          not this is an organic cation, or via P-glycoprotein,  
17          Cimetidine is used as the traditional probe of the  
18          organic cation pathway. It has been shown to inhibit  
19          secretion of procainamide, Creatinine, and other basic  
20          drugs.

21                   Cimetidine caused an increase in the AUC  
22          of Dofetilide of 58 percent. And this, as I will show

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1 you, this was due primarily to a reduction in the  
2 renal clearance of Dofetilide.

3 This effect on Dofetilide renal clearance  
4 supports that the pathway is via the organic cation  
5 secretory path.

6 Theoretically other actively secreted  
7 organic cations could also affect Dofetilide  
8 secretion. This possibility was examined in the phase  
9 3 patient pharmacokinetic data base. This data of  
10 1,445 patients included 219 who were receiving organic  
11 cation substrates, and 20 who were receiving organic  
12 cation inhibitors.

13 There was no evidence of an interaction  
14 with substrates, but even with a small number of  
15 concomitant inhibitors, a decrease in clearance of  
16 14.6 percent was suggested.

17 Targeted studies of commonly used organic  
18 cations should be considered to be performed.

19 This slide shows the data, these are the  
20 data from the Cimetidine study showing the inhibition  
21 of Cimetidine on Dofetilide clearance. There is a  
22 total decrease in clearance of 36 percent from a value

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1 of 484 to 308. There is a minor effect on non-renal  
2 clearance, and you will see that the substantial  
3 effect is on renal clearance, as is shown in the blue  
4 column here.

5 Let's now address the question of whether  
6 the P-glycoprotein pathway might be involved.

7 P-glycoprotein transport seems unlikely  
8 since Dofetilide was not transported by Caco 2 cells.  
9 In addition Verapamil, a potent P-glycoprotein  
10 inhibitor had negligible effects on overall clearance.

11 These comments notwithstanding, this area  
12 may warrant further study with other P-glycoprotein  
13 inhibitors.

14 Ketoconazole inhibited renal clearance,  
15 and I will show you those data in a moment. And  
16 though Ketoconazole is conventionally thought to  
17 inhibit P-glycoprotein, in addition to inhibiting  
18 CYP3A4, there is also evidence that it, and  
19 fluconazole can inhibit organic cation secretion.

20 Thus the Ketoconazole data are still  
21 consistent with organic cation secretion, though this  
22 area may also warrant further study, assessing the

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1 effects of Ketoconazole on other organic cation  
2 substrates.

3 The phase 3 pharmacokinetic data were also  
4 queried to see if there was a signal for interactions  
5 with P-glycoprotein substrates or inhibitors. In this  
6 data base were 658 patients receiving P-glycoprotein  
7 substrates, and 239 patients receiving inhibitors.  
8 There was no evidence of a clinically important  
9 interaction with either group of drugs.

10 Let's now turn to the component of the --  
11 the metabolic component of Dofetilide's elimination on  
12 the next slide.

13 Metabolism is a minor pathway of  
14 elimination compared to the kidney, accounting for  
15 about 30 percent of a dose. The metabolites are at  
16 such low concentrations that they have not been  
17 quantifiable in plasma, they have negligible intrinsic  
18 activity, the potency is less than 5 percent, and  
19 therefore they do not contribute to activity.

20 Dofetilide has negligible affinity for CYP  
21 iso enzymes, other than CYP3A4. A variety of in vitro  
22 and in vivo studies indicate that CYP3A4 is the iso

1 enzyme of interest in Dofetilide metabolism.

2 The low affinity of Dofetilide for CYP3A4  
3 predicts lack of inhibition of the metabolism of other  
4 substrates of this iso enzyme. This has been  
5 confirmed by a variety of clinical trials, and I will  
6 list those subsequently.

7 Ketoconazole, a very potent CYP3A4  
8 inhibitor, and I presume we would all accept the most  
9 potent inhibitor available today, caused a 55 percent  
10 increase in exposure to Dofetilide. Part of this was  
11 attributable to inhibition of metabolism, and part  
12 attributable to decreases in renal clearance. The  
13 data are shown on the next slide.

14 This slide shows the effect of  
15 Ketoconazole on both renal and non-renal clearance,  
16 and the data are shown in the table incorporated in  
17 the slide.

18 As discussed previously, the effect on  
19 renal clearance, which is the dominant component here,  
20 appears to be via inhibition of organic cation  
21 secretion.

22 The potency of Ketoconazole means that the

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1 magnitude of effects seen here likely represents the  
2 maximal inhibition of CYP3A4 that might occur with any  
3 other interactants via a metabolic pathway.

4 Ketoconazole decreases non-renal  
5 clearance, shown here on the table, by about 50  
6 percent. Since non-renal clearance represents about  
7 30 percent of total clearance, this amounts to an  
8 approximate 15 percent decrease in total clearance  
9 that can be attributed to the metabolic effect.

10 This value serves as a reasonable frame of  
11 reference when considering the potential impact of  
12 other drugs that might inhibit CYP3A4 to a lesser  
13 degree.

14 We also queried the phase 3 population  
15 pharmacokinetic data for -- to see if there was a  
16 signal for interactions with drugs that are either  
17 substrates or inhibitors for the CYP3A4 pathway.  
18 There were 108 patients receiving substrates, 27  
19 patients receiving inhibitors. There were no signals  
20 of a clinically important interaction in that data base.

21 The next slide summarizes these  
22 interaction data. On the left grouping is a group

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1 disappointing.

2 One of the things that one could speculate  
3 about, and this is pure speculation, is that there are  
4 probably mechanistic differences between paroxysmal  
5 and persistent atrial fibrillation. At least in a  
6 substantial percentage of patients.

7 And there is now increasingly impressive  
8 data on the role of focal tachycardias from the  
9 pulmonary veins as the primary triggers of paroxysmal  
10 AF. And if that is the case one might not expect them  
11 to respond to a class 3 agent.

12 But that is very highly speculative, and  
13 I don't think it provides a comforting or absolute  
14 answer to that. I just don't have an answer.

15 DR. KOWEY: It really is a very important  
16 issue in labeling because physicians have to be warned  
17 that they don't have a hope of having this drug work  
18 for a population of patients they are used to  
19 treating.

20 DR. PRATT: I think that is correct, I  
21 think we have to go with the data, and the data that  
22 we have, that demonstrates efficacy is in people with

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SGE CONSULTANTS:

DR. RALPH D'AGOSTINO  
DR. PETER R. KOWEY

GUESTS:

DR. ARTHUR ATKINSON  
DR. J. THOMAS BIGGER

ALSO PRESENT:

DR. STEVEN RYDER  
DR. JEREMY RUSKIN  
DR. TILMAN FRIEDRICH  
DR. CRAIG BRATER  
DR. GLEN ANDREWS  
DR. BRADLEY MARSHANT  
DR. CRAIG PRATT  
DR. ROBERT TEMPLE  
MR. LARRY SASICH

1 where there is no effect of Dofetilide on this list of  
2 drugs, and that would be as is predicted from the in  
3 vitro studies.

4 In the middle are a list of drugs where  
5 there has been no effect demonstrated by them to have  
6 an effect on Dofetilide, and in addition the  
7 population pharmacokinetic analysis indicated no  
8 effect on these concomitant drugs.

9 On the right are the three drugs for which  
10 a significant interaction has been identified. Again,  
11 Cimetidine occurs through an effect on renal  
12 secretion, Ketoconazole through an effect on secretion  
13 plus inhibition of metabolism, and Verapamil, by  
14 affecting the rate of absorption.

15 A study of hormone replacement therapy has  
16 been completed in terms of all of the patients have  
17 been enrolled and completed the study, and the data  
18 are currently being analyzed.

19 The sponsor has also explored the  
20 influence of patient demographics and concomitant  
21 disease on pharmacokinetics. As noted previously,  
22 there is an extensive data base for doing so. There

1 have been pharmacokinetic evaluations in more than  
2 1,500 patients in phase 2 and 3, with over 10,000  
3 plasma concentration measurements.

4 Analysis of this data base indicates that  
5 neither age, heart disease, type of arrhythmia, nor  
6 hepatic impairment are independent predictors of  
7 Dofetilide clearance after accounting for renal  
8 function.

9 What about a gender effect? Dofetilide  
10 plasma concentrations were about 12 percent higher in  
11 young healthy female volunteers compared to men.

12 In one study specifically designed to  
13 assess gender differences in pharmacokinetics the  
14 gender difference could be completely explained by  
15 differences in body weight. However, in contrast,  
16 gender related differences were still seen in the  
17 larger population of pharmacokinetic data base  
18 collected in phase 3.

19 The concentration differences shown here  
20 would translate into a two to four millisecond higher  
21 QTc value in women than in men.

22 The next slide summarizes the

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1 pharmacokinetic features of Dofetilide. Dofetilide  
2 pharmacokinetics are predictable. This is reinforced  
3 in particular in the population studies.

4 In phase 3 variability among patients in  
5 clearance was 24 percent, after accounting for renal  
6 function. Again, after accounting for renal function.

7 That volume of distribution was 28 percent  
8 after accounting for body weight, and the residual  
9 variability was 27 percent. These values are small.

10 The pharmacokinetics are linear, and the  
11 multiple dose pharmacokinetics are predictable from  
12 single doses.

13 Consistent with a half-life of 10 hours,  
14 steady state is achieved within two to three days. As  
15 stated, between patient variability, and the  
16 pharmacokinetics is low after adjustment for renal  
17 function. It is clear that the dependence they are in  
18 is such that doses need to be adjusted in patients  
19 with decreased Creatinine clearance.

20 Following is a scheme to individualized  
21 dosing that was implemented in the phase 3 trials. As  
22 indicated, treatment is initiated in hospital with

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1 continued CG monitoring, a serum Creatinine is  
2 obtained, and by using the Cocockroft-Gault equation,  
3 creatinine clearance is estimated, and then dose is  
4 adjusted as shown here in this middle box.

5 This scheme adjusts doses in a fashion to  
6 account for the main determinant of the  
7 pharmacokinetic variability. Subsequently I will  
8 discuss considerations in pharmacodynamic variability.

9 The next slide shows how this dose  
10 adjustment performed in patients. This figure shows  
11 the average state plasma concentrations observed in  
12 patients in phase 3 studies, for the patients with  
13 normal on the right, and reduced renal function.

14 It includes patients in a renal substudy  
15 of Diamond, who were dosed according to the dosage  
16 algorithm, and patients in the two pivotal chronic  
17 atrial fibrillation studies who were randomized to  
18 receive 500 micrograms twice a day, some of whom  
19 received lower doses due to the reduced renal  
20 function.

21 The concentrations in patients with low  
22 renal function are within the range of values for

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1 those with normal renal function, so these bands are  
2 pretty much the same.

3 The dosing adjustment was introduced after  
4 the start of study 120, so a few patients with low  
5 Creatinine clearances received 500 micrograms twice a  
6 day. These are marked in blue in the middle column.

7 It is apparent that these concentrations  
8 were at the upper end of the range of concentrations.  
9 If dosing adjustment had been applied, these values  
10 would be half those that are shown, which would drop  
11 them down into the range with all of the other  
12 patients.

13 So it appears from this data that the  
14 dosing individualization scheme works as it should.

15 We now turn to the pharmacodynamic aspects  
16 of Dofetilide effects. Firstly, some of its  
17 hemodynamic effects. As a PRKR blocker, Dofetilide  
18 would not be expected to have a negative anotropic  
19 effect.

20 This has been demonstrated in two invasive  
21 clinical studies of patients with left ventricular  
22 impairment. Study 127, which is shown across the top

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1 of this slide, was performed by Dr. Risseau in  
2 Belgium. These investigators randomized 32 patients  
3 with heart failure, and LVEF's less than 35 percent,  
4 to Dofetilide or placebo given intravenously.

5 Study 105, which is shown across the  
6 bottom, was performed in the U.S. In this study 29  
7 patients were randomized, they had ventricular  
8 tachyarryhtmias, and left ventricular ejection  
9 fractions between 20 and 30 percent.

10 They received either Dofetilide 250  
11 micrograms three times a day, 500 three times a day,  
12 or placebo.

13 All patients were in sinus rhythm in both  
14 of these studies. There is no negative effect on  
15 cardiac index, small increase in left ventricular  
16 ejection fraction, and no change on the right, in  
17 systemic vascular resistance.

18 Data from study 120 in patients with  
19 atrial fibrillation show the effect on hemodynamics  
20 when patients are converted to sinus rhythm. Cardiac  
21 index is preserved, shown on the left panel, despite  
22 a reduction in heart rate, shown in the red line,

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1 associated with the conversion from atrial  
2 fibrillation to sinus rhythm.

3 Since Dofetilide is an IKR inhibitor, it  
4 is predictable that it will affect the QTc interval.  
5 And, indeed, there is a direct relationship between  
6 QTc and plasma Dofetilide concentrations shown here.

7 So on the X axis we have mean Dofetilide  
8 concentration. On the Y axis we have change from  
9 baseline and QTc.

10 After a single dose, which is shown in  
11 blue, the slope is approximately 15 to 20  
12 milliseconds, and this relationship has been confirmed  
13 in the population studies.

14 Attenuation to sensitivity occurs during  
15 the first few days of dosing, where in a steady state,  
16 shown in red, the slope is about 10 milliseconds per  
17 nanogram, per milliliter.

18 Of note, the horizontal bar shown in this  
19 graph is white, it may be a little difficult to see,  
20 is that it represents the concentrations achieved with  
21 a 500 microgram BID dose.

22 Despite this good relationship some

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1 patients are likely to have greater sensitivity. As  
2 such, incorporated into the dosing regimen is a step  
3 to account for pharmacodynamic variability, as shown  
4 in the next slide.

5 The top part of this slide I've shown you  
6 before, and after dose adjustment occurs on the basis  
7 of renal function, patients are -- again have  
8 consideration for dose adjustment based on their own  
9 response.

10 So if the QT/QDC is prolonged greater than  
11 15 percent, or goes to a total duration of greater  
12 than 500 milliseconds, then the dose is, again,  
13 decreased to half over and above any reduction that  
14 was based on changes in renal function.

15 Since concentration correlates well to  
16 QTc, one might also predict a correlation with  
17 response. Our last slide examines this relationship  
18 in terms of looking at the effects of QTc and how they  
19 relate to efficacy.

20 So in the columns we have the probability  
21 of remaining in normal sinus rhythm at six months, and  
22 in the lines, the vertical lines, are the change in

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1 QTc interval from base line.

2 And you can see that each has  
3 approximately the same slope indicating a relationship  
4 here.

5 I hope that these last couple of slides,  
6 in particular, will serve as the basis for your  
7 thoughts in terms of thinking about the efficacy and  
8 safety of this drug.

9 And that concludes my comments about the  
10 clinical pharmacology of Dofetilide.

11 ACTING CHAIRMAN CALIFF: Thank you. This  
12 is a lot of information. Again, I would like to give  
13 Dr. Kowey and Dr. Grines a chance to ask the first  
14 questions, and then we have Dr. Atkinson as a special  
15 consultant, who I think will -- we are going to look  
16 to for a lot of help here.

17 DR. KOWEY: Craig, the reason why this is  
18 such an important discussion, it seems to me, is that  
19 there is this linear relationship between plasma  
20 concentration QT effect, efficacy, and Torsade.

21 And so I think this is really a critical  
22 part of the discussion. One of the things I'm having

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1 some difficulty with is drug interactions, and maybe  
2 you can help me.

3 What you've said is, basically, that if  
4 you take the most potent inhibitor, CYP3A4, that we  
5 know of, which is Ketoconazole, and you estimate its  
6 renal effect vis a vis its non-renal effect on  
7 metabolism, as a gross estimate, that it is somewhere  
8 in the vicinity of 15 to 20 percent, maybe closer to  
9 15 percent of its potentiating effect of Dofetilide is  
10 hepatic, or likely to be, non-renal.

11 And then if we then go backwards we could  
12 say that there is lots of other inhibitors of this  
13 enzyme system that we wouldn't expect them to be as  
14 potent.

15 Do we have to worry about that? I mean,  
16 do we have to go back and actually look at some of  
17 these drugs, antibiotics for example, that might  
18 influence that enzyme system? Because it is an  
19 assumption which I think is probably correct, but I'm  
20 a little concerned about it, because the stakes are  
21 pretty high here.

22 DR. BRATER: I guess you could approach it

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1 in two ways. You could either say, if you indeed  
2 believe that Ketoconazole is the biggest effect you  
3 are going to see, you could say, okay let's be  
4 ultraconservative and say, all the other things that  
5 inhibit that iso enzyme, let's just presume that they  
6 are going to have a similar effect and label  
7 accordingly.

8 Alternatively, you could go back and try  
9 to define, with more precision, by individual trials  
10 with some of those different drugs, and try to map out  
11 the degree of effect that is going to occur.

12 And I think that, in turn, is probably  
13 going to boil down into the thought process that you  
14 all have about the width of the therapeutic margin  
15 here, and how that leads you down either of those  
16 paths.

17 DR. KOWEY: You see, I don't think there  
18 is a whole lot of room, and that is why I'm having  
19 this problem, and we are going to be faced with -- and  
20 if you look down through the questions, you always do  
21 that to find out what the bottom line is going to be  
22 here, we are going to be asked a question, at the end

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1 of the day, are there other studies that need to be  
2 done.

3 DR. BRATER: Right.

4 DR. KOWEY: And my concern is that if we  
5 don't have studies, I think you are absolutely  
6 correct, that if we don't have a study of a drug  
7 interaction, and a drug which is in the category of a  
8 drug that blocks that enzyme system, and a drug that  
9 has a fairly narrow margin for safety, that we are  
10 going to have to make the worse case assumption, and  
11 label the drug so that every single drug on that long,  
12 long list is put into the labeling as being a problem,  
13 and the drug needs to be dosed accordingly.

14 Is that -- I may have paraphrased what  
15 you have already said.

16 DR. BRATER: I'm saying the same thing you  
17 are. And the same thing, it goes to the cationic  
18 secretory pathway. We have data with Cimetidine.  
19 There are -- that is a short list of potential  
20 inhibitors there, but so the question is, do you take  
21 Cimetidine as the worse, and then presume everything  
22 else is -- and lump everything else in that category

1 or do you do specific studies.

2 So it is exactly the same thought process.

3 ACTING CHAIRMAN CALIFF: Dr. Grines?

4 DR. GRINES: A couple of questions on the  
5 hemodynamic effects. And one is on the bar graph you  
6 showed for ejection fractions. I wondered if you knew  
7 the sample size?

8 DR. BRATER: Is this the hemodynamic data?

9  
10 DR. GRINES: The hemodynamic effects of  
11 normal sinus rhythm.

12 DR. BRATER: No, I don't know the sample  
13 size, approximately 25 patients.

14 DR. GRINES: 25 patients. Yes, because it  
15 seems like there is a huge increase in ejection  
16 fraction, and that is hard to --

17 DR. BRATER: That is percent of a percent,  
18 I believe. That is not an absolute -- all the changes  
19 on that graph are percent changes.

20 DR. GRINES: It looks like an absolute  
21 ejection fraction, actually, the way it was plotted.

22 The second question on the dosing

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1 individualization, there is recommendations for  
2 cutting to half dose if the QT interval is prolonged.  
3 But in the study actually several patients were  
4 completely discontinued due to QT prolongation, and I  
5 wondered, with regard to these QT intervals, at what  
6 level of prolongation would you recommend completely  
7 discontinuing the drug, and how often does one have to  
8 measure this?

9 DR. BRATER: I can't answer the first part  
10 of your question, you are going to have to depend on  
11 your cardiology colleagues, I think, to answer the --  
12 you know, where you would absolutely quit the drug in  
13 terms of what QT. I'm a poor country clinical  
14 pharmacologist, so I don't know that.

15 But the other question, you had another  
16 part to your question, which was --

17 DR. GRINES: I guess I'm just a little  
18 confused.

19 DR. BRATER: The stability of the QT. I  
20 haven't seen the data myself, but I'm told that the QT  
21 is very stable in terms of its relationship to plasma  
22 concentration throughout the course of therapy.

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1           ACTING CHAIRMAN CALIFF: Will we have a  
2 chance to see that data later on about the stability  
3 of the QT? Okay.

4           DR. BRATER: I see people nodding their  
5 heads yes.

6           DR. GRINES: It is my recollection that in  
7 the studies the QT interval was measured just after  
8 the first dose, is that correct? And so, therefore,  
9 does that mean you don't have to measure it  
10 subsequently if it is stable?

11           DR. BRATER: My recollection is that the  
12 greatest prolongation is, as one might predict, which  
13 is about the peak time after the first dose, which is  
14 when you have your greatest sensitivity, and thus your  
15 plasma concentrations are coming up, so it is two to  
16 three hours after the first dose.

17           But I think the dosing recommendation is  
18 to monitor throughout this three day period, and make  
19 sure that if there are others that exceed that, that  
20 those are ones that are taken into account in terms of  
21 changing the dose.

22           DR. KOWEY: Can I just follow up on that

1 a little bit, Craig, because it will come into some  
2 practical concerns with a poor country cardiologist  
3 using the drug.

4 If you start somebody on the drug at a  
5 dose level that is calculated based on the creatinine  
6 clearance, and you have the patient in the hospital,  
7 monitoring their rhythm, and their QT interval, is it  
8 three whole days before you can say that you don't  
9 have to do anything more with the dose because the QT  
10 interval didn't prolong, or can you get away with a  
11 shorter period of time?

12 DR. BRATER: My bias is that they ought to  
13 be in there for three days of therapy on Dofetilide.  
14 And one of the reasons for that is from a  
15 pharmacokinetic -- a lot of these patients are going  
16 to have decreased renal function, and their half-lives  
17 are going to be longer, and so you want to make sure  
18 that they are in there long enough to get the steady  
19 state.

20 So in that group of patients with the  
21 lowest level of renal function, 20 to 40, their half  
22 life is about 21.7 hours. And so the three days will

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1 get them like 90 percent to steady state.

2 So if for no other reason they ought to be  
3 in for three days just to make sure you capture that  
4 group of patients.

5 DR. KOWEY: And then after that, let's say  
6 for the sake of argument, I've cut the dose based on  
7 a QT prolongation that is protocol defined, and you  
8 are now down at a lesser dose level, do you keep them  
9 for three more days to make sure that at that steady  
10 state plasma concentration their QT is going to go  
11 back; or do you say, that should be enough, I can send  
12 them home now?

13 DR. BRATER: Well, I hadn't thought about  
14 that, but I -- just off the cuff, I would say that  
15 like most things it is probably going to be a clinical  
16 judgement, which might impart, do you know how long  
17 did it go out, did it go out 16 percent? And that  
18 triggered it, or did you -- you know, did it go out  
19 further and so you are more worried and you make sure  
20 you want to really follow that patient more closely.

21 So I guess you would have to dial that  
22 into the individual patient. I don't know if

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1 recommendations have been thought of in terms of that  
2 scenario.

3 DR. KOWEY: This is -- it occurred to me  
4 in the middle of reading this, I was trying to go  
5 through, well what is, as I said, try to just be an  
6 old country cardiologist, and I'm in the hospital, and  
7 I have a patient, I put them on the drug.

8 I think we have to be a little bit more  
9 definite about what the recommendations are going to  
10 be, as we dial back the dose. Because this is a very  
11 novel way of dosing, as you know, with an  
12 antiarrhythmic drug. We don't dose antiarrhythmic  
13 drugs this way. We do with Amiodarone, but nobody  
14 knows what the right dose is there, anyway, so that  
15 doesn't matter.

16 But here we do think we know what the  
17 right dose is, and we are going to be giving very  
18 specific instructions about a very novel way of dosing  
19 the drug to people who aren't used to using this drug,  
20 and doing it this way.

21 So I guess what my question is, do we have  
22 to maybe do some studies, or do we have to think about

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1 this some more to come up with a way of approaching  
2 this?

3 Because I'm very uncomfortable not being  
4 able to tell people how to do this. Does anybody  
5 else, on the panel, because I haven't been able to  
6 figure this out. Or does anybody else from the  
7 company want to respond?

8 ACTING CHAIRMAN CALIFF: Peter, let me  
9 suggest that we -- I mean, I think when we hear the  
10 efficacy data wed be a better time to discuss this.

11 DR. KOWEY: It is not in there, Rob. I  
12 mean, you can wait until the end of the day if you  
13 want to, but I'm telling you that we don't have those  
14 kinds of data in the -- I haven't seen it, maybe they  
15 are going to present something. If you want to wait,  
16 that is fine.

17 ACTING CHAIRMAN CALIFF: I really would  
18 rather wait, because if we get into this discussion  
19 now, we are going to have to repeat it at the end of  
20 the day anyway, about the practical. Okay?

21 AUDIENCE MEMBER: Dr. Kowey, just some  
22 information. The clinical trials, what was done, when

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1 dose adjustment occurred, you want to be sure that the  
2 patient is in sinus rhythm so you would keep the  
3 patient at least one day in the hospital while the  
4 patient is in sinus rhythm.

5 DR. GRINES: I have one other question.  
6 You showed a graph, it is titled the concentration  
7 relationship in young volunteers over 24 days. And in  
8 that graph I think you described an attenuation of the  
9 QT interval?

10 DR. BRATER: Correct.

11 DR. GRINES: Basically the QT was longer  
12 on day 1 than it was on day 23. And my question is,  
13 are we going to be able to safely monitor the chronic  
14 effects looking at the QT interval? Because on the  
15 bar graph you see that now we have much higher doses  
16 of drug with the shorter QT interval.

17 Now, is the incidence of Torsade related  
18 to that QT interval, or is it related to the dose of  
19 the drug?

20 DR. BRATER: Well, when you -- let's flash  
21 that slide back up there, that is slide number 19.  
22 Just as a frame of reference.

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1 I think one of the questions that you are  
2 asking, and make sure if I'm going in the wrong  
3 direction you correct me, is that basically I think  
4 one of the questions will be, how quickly does that  
5 occur, and how stable is it once you get down there?

6 If we call back up 96, this shows the time  
7 course of this decrease, so in black is Dofetilide and  
8 you see, and these are the same patients from which  
9 that previous figure is derived.

10 You see that basically you start getting  
11 this decreased sensitivity by the second dose, and you  
12 come out here and you plateau out very quickly, and it  
13 is very stable.

14 So I guess it is the stability of this  
15 plateauing effect that I think would -- isn't that the  
16 answer to your question?

17 DR. GRINES: Well, I guess my real  
18 question is, how confident are we at decreasing the  
19 dose, or discontinuing the drug based on the QT  
20 prolongation, if the QT interval is going to change  
21 over time?

22 DR. BRATER: I guess that gets back to the

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1 question, again, of what is the stability of the QT  
2 throughout the time course of therapy, say six months,  
3 or something. I don't personally have those data, but  
4 I saw nods that that was going to be addressed by  
5 somebody else.

6 DR. GRINES: Because the dose can be --  
7 the dose for a given QT interval, you can have a much  
8 higher dose, chronically. And if the Torsade is  
9 related to a high dose, then perhaps we could be  
10 having some late arrhythmias, even though the QT  
11 interval may look relatively normal.

12 DR. BRATER: Say that again? I'm not  
13 following --

14 ACTING CHAIRMAN CALIFF: Maybe I could try  
15 to -- I think what you are asking is, is the risk of  
16 Torsade more closely related to the QT interval, or to  
17 the concentration?

18 DR. GRINES: Correct.

19 DR. BRATER: Well, my cardiology  
20 colleagues tell me that the main reason for following  
21 QTs is because of -- is because the Torsade risk, that  
22 you wouldn't be following it as an efficacy predictor,

1 but basically as a safety monitor.

2 And I guess what we are saying is, that  
3 the concentration seems quite tightly linked to the  
4 QTc interval, so then for example, if you are going to  
5 think about monitoring the patient, it makes more  
6 sense to monitor the QT than it does to, say, monitor  
7 the plasma concentration.

8 ACTING CHAIRMAN CALIFF: Dr. Bigger, do  
9 you have a comment on that?

10 DR. BRATER: Because that is closer to the  
11 end point of adverse effect.

12 DR. BIGGER: I have a question right along  
13 that line, on that slide 19, in that very nice slope  
14 of the QT change on the dose, or the concentration of  
15 Dofetilide. If you are in a steady state, and you  
16 alter the serum potassium substantially, say with  
17 diuretics, or something else, in a current diarrhea,  
18 or whatever, does that slope shift up or down, or is  
19 it sensitive to changes in potassium that might occur  
20 in the usual course of events in people with heart  
21 failure and so forth?

22 DR. BRATER: I don't know that that study

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1 has been done. I didn't see it in anything that I  
2 reviewed, but it could have escaped me. The best I  
3 can say is that there, I think in the supplement that  
4 went out, there was a pretty detailed analysis of risk  
5 of Torsade and of mortality according to a whole lot  
6 of concomitant medications in substantial numbers of  
7 patients, as you would expect, who were on diuretics,  
8 both thiazides and loops.

9 And my understanding of those data is that  
10 there was no -- that is epidemiological data that  
11 there was no signal that there might be an increase in  
12 mortality, or Torsade. But that is not a direct  
13 answer to your question, of course.

14 DR. BIGGER: The pharmacokinetic question  
15 I have, in Diamond CHF, I think over 90 percent of the  
16 people who are taking diuretics. But it didn't  
17 differentiate which kinds, and I wondered, since the  
18 different diuretics posited in different segments, and  
19 tubal, if there is any relationship to particular  
20 diuretics, or diuretic combinations that might affect  
21 the renal clearance of Dofetilide?

22 DR. BRATER: Well, the potassium sparing

1 diuretics, amiloride and triamterene, not  
2 spermalactone, but amiloride and triamterene are  
3 organic cations that are secreted by the nephron.

4 So there is a potential for -- and a  
5 pharmacokinetics interaction there. But I wouldn't  
6 suspect a pharmacokinetic interaction with thiazide or  
7 loops.

8 ACTING CHAIRMAN CALIFF: I want to give  
9 Dr. Atkinson a chance. And what I would urge, based  
10 on what I've heard so far, would it be correct to say  
11 that, Dr. Brater, you are not going to answer clinical  
12 cardiology questions, but renal questions of  
13 pharmacokinetic, or pharmacodynamic questions you are  
14 prepared to answer?

15 DR. BRATER: That's correct.

16 DR. ATKINSON: Thank you, Dr. Califf. I  
17 would like to ask a few questions, because I probably  
18 will be silent for the rest of the presentations.

19 I think, Craig, first of all you have  
20 summarized an awful lot of very interesting data very  
21 elegantly for us today.

22 DR. BRATER: Thanks.

1 DR. ATKINSON: But, really, all the  
2 nuances of drug interactions, and variability, and  
3 pharmacokinetics, have an importance, really, that  
4 relates only to the therapeutic index of the drug.

5 And I think we've heard from the  
6 floor, earlier today, that there is general concern  
7 between the therapeutic, the levels or dose that may  
8 cause therapeutic efficacy, and those that cause  
9 toxicity.

10 And I wonder if you have, or the company,  
11 has any data on therapeutic index, not necessarily  
12 relating to the QTc interval prolongation, but Torsade  
13 which is the main concern here.

14 DR. BRATER: It is clear, from the data I  
15 have shown you, that there is a good relationship  
16 between concentration and QT, and if QT is the  
17 predictor of Torsade, you might expect that well gee,  
18 we ought to see a good relationship here than between  
19 concentration in plasma and Torsade.

20 The problem, I guess, is that there are so  
21 few patients in the data base with Torsade, that you  
22 can't really do that analysis now. There has been an

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1 attempt to look at analysis between relating  
2 concentration to efficacy in terms of maintaining  
3 normal sinus rhythm.

4 I showed you the relationship between QT  
5 and normal sinus. That is also a difficult one  
6 because it is, in my simplistic approach to things I  
7 thought, well, we can just do some sigmoid max plot of  
8 CP versus response, but I was shot down by  
9 biostatisticians and said, you have to do a Kaplan-  
10 Meier approach, because these are categorical data  
11 which makes that much more difficult.

12 That analysis has been done. To me that  
13 shows a relationship. I can show it to you, if you  
14 would like.

15 DR. ATKINSON: I would like to see it.

16 DR. BRATER: That is backup slide 203. So  
17 here on the X axis we've got these categorical data of  
18 different serum concentration values, probability of  
19 remaining in normal sinus rhythm, similar to what I  
20 showed you with the QTc normal sinus rhythm thing.

21 And at least to my eye, you see this  
22 coming up and plateauing out.

1 DR. ATKINSON: Thank you. From my  
2 calculations I would estimate that the sponsor intends  
3 to recommend the dose that would achieve effective  
4 concentrations for maintenance.

5 DR. BRATER: Well, if we could have that  
6 slide back, I guess we could put a frame of reference  
7 where the 500 microgram BID would be out in this  
8 range.

9 DR. ATKINSON: Exactly, and that is with  
10 appropriate adjustment for renal functional status?

11 DR. BRATER: Right. So patients who had  
12 decreased renal function, if they were supposed to get  
13 500, and you down titrated it, I think I showed you  
14 data that shows that that keeps those patients in the  
15 same kind of concentration range, so they would be in  
16 the same kind of bar.

17 DR. ATKINSON: Is there evidence to  
18 suggest that the levels required for initial  
19 cardioversion from atrial fibrillation might be  
20 different than those required for maintenance? Or is  
21 that not --

22 DR. BRATER: I don't know that that

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1 analysis has been done. That is not been looked at.

2 DR. LIPICKY: Before that slide goes away  
3 if you would show that slide again? If you believe  
4 that data, where would you put the EC50 for the  
5 therapeutic effect?

6 ACTING CHAIRMAN CALIFF: For the audience,  
7 could you define AC50?

8 DR. LIPICKY: The concentration at which  
9 about 50 percent of the efficacy effect occurred, or  
10 about 50 percent of the patients would have a good  
11 effect from the drug.

12 DR. BRATER: Well, that is why I wanted  
13 them to do a sigmoid max kind of thing, but they said  
14 you can't do that. But if I look at my eyeball, and  
15 subtracted out placebo, and looked at that curve I  
16 would say, maybe you are in the 1.3 to 1.7 bar.

17 DR. TEMPLE: No, it is below .4, it is  
18 below .4, the lowest concentration gives you the easy  
19 50, obviously. To the extent you believe all that,  
20 anyway. If you are going from 50 percent to 60  
21 percent, or 30 percent to 60 percent.

22 DR. THADANI: The mode will be between the



1 first three lines.

2 DR. BRATER: Well, I don't know, this plot  
3 looks to me to be up around 65 or 70, right?

4 DR. TEMPLE: Well, that is the plateau  
5 that goes after .4, but most of the action is between  
6 zero and .4.

7 DR. BRATER: Well, but if you are do an  
8 easy 50 you map out the whole curve, right? And then  
9 you say how long does it take to get -- where do you  
10 need to be to be 50 percent up there.

11 DR. TEMPLE: But the lowest concentration  
12 is more than 50 percent of the effect.

13 DR. LIPICKY: And where is the EC50 for  
14 the QT? You know that very well.

15 ACTING CHAIRMAN CALIFF: This is, I think,  
16 going to be the central discussion, and I hate to  
17 think we are going to be left with us all eyeballing  
18 this bar graph and coming to conclusions.

19 So during the course of the day we need to  
20 come to some better resolution of --

21 DR. ATKINSON: Having raised the specter  
22 of therapeutic index can I focus now a little bit on

1 pharmacokinetics?

2           You've shown a very good relationship  
3 between overall clearance of the drug, and estimated  
4 creatinine clearance. And I believe your correlation  
5 coefficient squared was .84.

6           There are other equations that appear, as  
7 different studies, as you might expect. One point I  
8 would like to make is that although you emphasized  
9 that normally non-renal elimination is minor, it  
10 accounts for only 30 percent of elimination, obviously  
11 as renal function becomes impaired, non-renal function  
12 becomes more important.

13           And what seems to be unusual, at least  
14 from my calculations here, is that this is a drug in  
15 which not only renal clearance declines with  
16 decreasing creatinine clearance, but non-renal  
17 clearance declines with decreasing creatinine  
18 clearance.

19           And I wonder if you or the sponsor have  
20 data that actually separate out? I know you've done  
21 the renal clearance of the drug versus creatinine  
22 clearance. Can you show us the variability in non-

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1 renal clearance now, as creatinine clearance declines?

2 DR. BRATER: If we bring up backup slide  
3 11. Went back to some of the previous studies and  
4 calculated total clearance, renal clearance, and non-  
5 renal clearance at the different levels of renal  
6 function.

7 The patients on the far right would be  
8 recommended to be excluded from therapy. So the ones  
9 in the middle, which would be the lowest, non-renal  
10 clearance drops from 7.8 to 5.6. But, as you point  
11 out, becomes a substantial component of the overall  
12 clearance, probably three quarters or more of overall  
13 clearance.

14 So there is, clearly, a decline in non-  
15 renal clearance with decreasing renal function. That  
16 is not unprecedented, as you know, that is seen with  
17 other drugs. We don't know the mechanism for that,  
18 but it certainly does occur with Dofetilide.

19 And you can also see that by the slope,  
20 the intercept of the slope of those relationships if  
21 you look close.

22 DR. ATKINSON: That brings me to another

1 point. By looking at the intercept of the slope we  
2 are, in fact, extrapolating from a curve that has been  
3 incompletely characterized.

4 And one obvious deficiency that I saw in  
5 an otherwise detailed kinetic package is that there is  
6 no study, at least that I'm aware of, of Dofetilide  
7 kinetics and functionally nephric subjects.

8 I mean, here is the population where non-  
9 renal clearance accounts for 100 percent of  
10 elimination, and I think I may have seen, in fact, a  
11 draft package insert where the recommendation for  
12 patients with creatinine clearance less than 20 is to  
13 individualize the dose.

14 And I submit that if you don't have an  
15 estimate of what the clearance is for those patients,  
16 it is awfully hard to individualize the dose, using  
17 the paradigm that you recommend.

18 DR. BRATER: I think that gets to one of  
19 the questions that you all will be faced with later in  
20 the day.

21 DR. ATKINSON: Okay. Another question  
22 that I think is germane to the proposed strategy of

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1 individualizing dose based on creatinine clearance is  
2 the extent to which creatinine clearance is  
3 determined, or estimated, if you will, from the  
4 Cocockroft-Gault equation in hospitalized patients.

5 I wonder if you could give us an estimate,  
6 from your medical center in Indiana, as to how many  
7 patients in the hospital really have their creatinine  
8 clearance estimated?

9 DR. BRATER: I guess it depends on who is  
10 your attending that month. When I'm attending, every  
11 one of them.

12 I think that is a rhetorical question, but  
13 you are asking about the awareness of the potential  
14 users of this algorithm. And I think that is an issue  
15 that needs to be considered in terms of how that kind  
16 of education is going to occur, and even questions  
17 like should it be -- you try to get people to remember  
18 an equation like that, or should you develop a little  
19 nomogram that we've all seen, where you just have to  
20 lie a straight edge across something, and that helps  
21 give you the dose.

22 There are a lot of different ways to

1 slice, to try to slice that cake. But the bottom line  
2 is that you are going to have to educate people on how  
3 to estimate renal function in patients who are going  
4 to receive this drug, and adjust the dose.

5 DR. ATKINSON: I would submit to you that  
6 educational efforts are not terribly effective. I  
7 mean, this may be that I'm a poor teacher, but I  
8 haven't had much success with it. And, in fact, it  
9 seems -- and I will pass this on to the company, it  
10 seems inappropriate in this day and age of computers  
11 to expect busy physicians and pharmacists, and nurses,  
12 to do these trivial calculations themselves.

13 The real problem here is that clinical  
14 chemistry laboratories report serum creatinine  
15 measurement which in many cases is frankly misleading.  
16 There are patients with grossly abnormal renal  
17 function that have normal serum creatinine values.

18 Someday, hopefully, we will get the  
19 hospital data systems to bring the patient age, and  
20 body weight, and gender together with the serum  
21 creatinine number, and actually calculate the  
22 creatinine clearance or estimate it automatically.

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1                   But that may work better for the company  
2 to focus on, than trying to continue educational  
3 efforts. And I think, Craig, you and I both will say  
4 have largely been futile.

5                   DR. BRATER: Yes, well, and we have  
6 electronic medical record that we can actually feed  
7 that to our doctors, and that is the ultimate  
8 solution.

9                   DR. ATKINSON: Those are the questions  
10 that I have at this point.

11                   ACTING CHAIRMAN CALIFF: Thank you. What  
12 I would like to do is give the right side of the table  
13 a chance to ask some questions, to start with, and  
14 work back around.

15                   DR. LINDENFELD: I have a question. The  
16 relationship you showed between QTc and Dofetilide  
17 concentration, is that slope the same in the elderly  
18 with age, and with women versus men?

19                   DR. BRATER: So the question is both  
20 gender and age?

21                   DR. LINDENFELD: Right. Which I think is  
22 particularly important in the population of patients

1 we are considering here.

2 DR. BRATER: Yes. There is data on that.  
3 Let's first have the backup slide that shows it  
4 according to gender. I'm trying to find the number  
5 here. How about backup slide 99.

6 This looks at the slope. Now, this is  
7 single dose slope, so it would be the higher value  
8 that I mentioned. And so here is the slope in young  
9 men, young women, elderly as opposed to young.

10 And this was noted in the elderly study,  
11 that they might have, actually, a decreased  
12 sensitivity. But you see all of the numbers are  
13 reasonably consistent.

14 DR. LINDENFELD: I know this might be  
15 difficult, but can you give me some idea of what this  
16 elderly population consists of, the age range, or the  
17 median age, or something, and what was considered  
18 elderly?

19 DR. BRATER: Yes, we actually have that.  
20 Backup slide 73, I think, would show that. I don't  
21 know if this is the graphical presentation. How about  
22 74? That is the graphical presentation, I believe.

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1           So here is the age distribution, it is  
2           pretty broad, a lot of elderly people.

3           DR. LINDENFELD:    Second question, in  
4           pharmacodynamics. Do you have any data on the -- we  
5           had some concerns, I noticed, in the packet, about  
6           blood pressure, and heart rate in patients on beta  
7           blockers, and also patients on diltiazem.

8           DR. BRATER: I don't on Diltiazem. Well,  
9           pharmacodynamics data on it. We've queried the  
10          population data base in terms of interactions with  
11          things like Diltiazem, and Diltiazem also fits in the  
12          3A4 category of potential inhibitor substrate, and did  
13          not see a signal for any interaction.

14          But there is a propranolol study.

15          DR. LINDENFELD: Right, and the blood  
16          pressure and heart rate dropped substantially on one  
17          of the patients.

18          DR. BRATER: Let me show you that.

19          DR. LINDENFELD: Let me show you that. So  
20          I would be concerned about Diltiazem, as well, with  
21          that.

22          DR. BRATER: Let me show you the

1 Propranolol stuff, because that is -- I think it is  
2 important to see what happened there. And we can do  
3 that very quickly.

4 Backup slide 54 shows the heart rate data  
5 with Propranolol. And this is subtracting out the  
6 base line, so this is changed from base line and heart  
7 rate. I mean, you see, it looks like there is a  
8 Propranolol effect.

9 I guess it depends on how you want to  
10 slide and dice this cake, because backup slide 55  
11 shows that if you just look at absolute effects on  
12 heart rate, absolute heart rate in these studies.

13 And so, clearly, what you are seeing on  
14 the first one was a different baseline. The same  
15 thing is true of blood pressure.

16 So whether or not there is an interaction  
17 here, it probably is debatable.

18 DR. LINDENFELD: Just my last question.  
19 Someone else may want to address this. How are QT and  
20 QTc intervals measured in this study, in atrial  
21 fibrillation? And I guess I want to comment --

22 DR. BRATER: You are going to have to have

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1 one of these other folks --

2 DR. LINDENFELD: -- both on how are they  
3 measured in terms of heart rate, and then how often  
4 could QTc actually be measured.

5 DR. BRATER: Well, in terms of heart rate,  
6 a bazetts correction was used. But in terms of the  
7 mechanics of how it was actually done in the studies,  
8 I think --

9 DR. LINDENFELD: I mean in atrial  
10 fibrillation the heart is often very irregular, that  
11 is what I'm getting at.

12 MR. MARSHANT: Brad Marshant, Pfizer  
13 Central Research. The QT interval was measured by  
14 instructing the investigator to select the most  
15 appropriate lead, and to use the same lead  
16 continuously throughout the study, and they were given  
17 guidance as to how to measure the end of the T-wave,  
18 and that was defined as the end of the T-wave, unless  
19 there was disturbance, abnormal T-wave morphology, in  
20 which case they were instructed to draw a tangent to  
21 the steepest portion of the T-wave, and where that  
22 tangent crossed the itroelectic line, that was the end

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1 of the T-wave.

2 In study 120 we gave careful instructions  
3 as to how the QT interval should be corrected for  
4 heart rate, and investigators were instructed to  
5 measure at least 10 beats of atrial fibrillation, and  
6 then work out the heart rate from there.

7 DR. LINDENFELD: So, in other words, in  
8 patients with atrial fibrillation you will be asking  
9 physicians to average the QTc interval over ten beats?

10 MR. MARSHANT: Correct.

11 DR. LIPICKY: And that has to include  
12 beats where the QT was measured?

13 MR. MARSHANT: Certainly, it would be  
14 important that the QT was measured during the interval  
15 that -- over which you are measuring the heart rate.

16 DR. LINDENFELD: Which in many cases there  
17 are not ten consecutive beats on our average current  
18 12 lead EKGs, depending on the heart rate. Just as a  
19 practical matter many 12 lead EKGs, which have all the  
20 beats right in a row don't have ten beats.

21 ACTING CHAIRMAN CALIFF: I know we are  
22 going to get back to this, but I guess the

1 recommendation of the sponsor that all patients be  
2 continuously monitored for three days would probably  
3 give you a rhythm strip.

4 But, then again, the question of which  
5 lead, it is an interesting set of issues.

6 DR. LIPICKY: You have left me with the  
7 impression, from the last slide you showed in your  
8 talk, that there is no safety margin. That is, if I  
9 look at the relationship between dose and QT, and dose  
10 and probability of being in sinus rhythm, if I want to  
11 be in sinus rhythm I have to have the QT go up.

12 And if I want a little better chance of  
13 being in sinus rhythm I have to have another increase  
14 in my QT. Is that the impression you want to leave,  
15 that I have no chance of having a beneficial drug  
16 effect without having a significant prolongation of  
17 the QT, and that there is no safety margin associated  
18 here?

19 DR. BRATER: Well, I think this is going  
20 to be discussed in agonizing detail with Craig Pratt's  
21 discussion, but I guess maybe this is an  
22 oversimplification of what you are saying, Ray, or

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1 asking.

2 If you are asking, is there a dose at  
3 which you can get efficacy and completely avoid risk,  
4 the answer is probably no. So like everything else,  
5 it is a ratio thing.

6 ACTING CHAIRMAN CALIFF: We will come back  
7 many times to this question, I'm sure. Other  
8 questions over here?

9 DR. LINDENFELD: Just quickly. Were many  
10 patients excluded because the QT could not be reliably  
11 measured in atrial fib, were there many patients  
12 excluded for that reason?

13 DR. BRATER: Brad is shaking his head no.

14 MR. MARSHANT: No, there weren't.

15 ACTING CHAIRMAN CALIFF: Dr. Konstam?

16 DR. KONSTAM: Yes, thanks. I wonder if  
17 you could put back up the slide labeled interaction  
18 studies? I think it is your number 11.

19 DR. BRATER: Slide number 11, please.

20 DR. KONSTAM: Yes, there it is. I guess  
21 I'm going to be looking for any help you can give us  
22 here, because this is another area where we are going

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1 to be concerned, given our past experiences with drug-  
2 drug interactions, and particularly here where there  
3 is going to be such a significant potential adverse  
4 effect if concentrations go up.

5 Can you just explain, again, what it took  
6 to get a particular drug in one of these boxes, what  
7 does it mean that a drug got into that second box with  
8 no effect on Dofetilide?

9 DR. BRATER: These are where studies were  
10 actually performed. So a focused interventional drug  
11 interaction study was performed where patients  
12 received Digoxin plus Dofetilide, and the effect of  
13 Dofetilide on Digoxin pharmacokinetics was examined.  
14 That is the same for all on this list.

15 So these are the result of directly  
16 performed studies addressing those questions.

17 DR. KONSTAM: What are the ends of such  
18 studies?

19 DR. BRATER: I don't know. What are the  
20 ends of those studies, on average? 24, maybe.  
21 Usually these studies are about 24 people.

22 DR. KONSTAM: Then is this the universe of

1 drugs on which these studies were conducted?

2 DR. BRATER: So that we have no useful  
3 information on any other drug besides the ones that  
4 are in this list, or definitive information?

5 DR. BRATER: Only indirect through the --  
6 what is a very rich population data base. These 1,400  
7 patients have had over 10,000 blood concentrations.

8 And let me stress that that should not --  
9 there is often a tendency, certainly I have it  
10 sometimes, to dismiss that kind of data. But there  
11 was clearly a Ketoconazole interaction, right, I  
12 showed you that.

13 If you take the patients from those  
14 Ketoconazole study, the end of 16, and if you dump  
15 that data into the data base of the 1,445, and then  
16 you do the population analysis and say, does it pick  
17 up a signal for a meaningful drug interaction, it  
18 does.

19 So that, you know, you get a signal that  
20 hey, Ketoconazole has an effect, and in turn that the  
21 effect on clearance, estimated by that population  
22 analysis is in the same range, 30 some percent, as in

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1 the interventional study.

2 So I do think that the population data  
3 base does, indeed, add some information.

4 DR. KONSTAM: Well, I mean, are we going  
5 to see that? In terms of negative -- so there are  
6 other drugs that you could draw up on that population  
7 to say that there is no effect on Dofetilide  
8 concentrations by the presence of that drug?

9 DR. BRATER: Yes, through the population  
10 data base. Now, does that mean, for example, we know  
11 that there is a cation pathway here. Does that mean  
12 that we would want to base our comfort level solely on  
13 that population analysis? My bias would be no.

14 I would say that, yes, we probably need to  
15 do another study or so with some other organic bases  
16 and map that out in a little bit more detail. And  
17 similar to where I think Peter was going with the 3A4  
18 inhibitors, do we need to do some specifically  
19 targeted studies there.

20 DR. KONSTAM: Okay, just a couple of  
21 specific questions, then, about it.

22 So you mentioned with cimetidine an effect

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1 on renal clearance, and you mentioned with Verapamil  
2 an effect on absorption.

3 DR. BRATER: Correct.

4 DR. KONSTAM: Can we anticipate that there  
5 are other drugs that would fall into those classes of  
6 interaction?

7 DR. BRATER: Being able to answer that  
8 question may require another, definitively, may  
9 require another study.

10 So, for example, one would presume, just  
11 from what we know about Verapamil and the way that  
12 interaction looked, that it is probably an effect of  
13 increasing the rate of absorption.

14 How might that happen? Well, it could be  
15 through increased blood flow to the gut. So then you  
16 would ask yourself the question, okay, what is another  
17 drug that we might look at that has the same  
18 pharmacologic effect and see if it does the same  
19 thing.

20 And then if it did not, then you would  
21 say, maybe this is because it was immediate release,  
22 and we need to look at sustained release, and maybe it

1 is a non-issue. Or, alternatively, it could be an  
2 issue with drugs that affect GI blood flow.

3 DR. KONSTAM: So are there other drugs  
4 that we have to worry about this --

5 DR. BRATER: Yes.

6 DR. KONSTAM: How many, and also with  
7 regard to the Cimetidine effect? I mean, is this a  
8 very unusual interaction?

9 DR. BRATER: No, it is nothing like you  
10 saw with Mibefradil. This drug isn't even close, at  
11 least in my opinion, I would be interested in what  
12 others have to say in terms of its potential as  
13 Mibefradil.

14 DR. KONSTAM: What other drugs can you  
15 think of that would have the Cimetidine effect?

16 DR. BRATER: Organic cations that are  
17 actively secreted are Metforman, Triamterene,  
18 Amelorida, Trimethraprine. Those would probably be  
19 the main ones. There are a few others, but they --  
20 Ethambutol, Amantadine, they are not used very much.

21 But that is a pretty short list.

22 DR. KONSTAM: Well, what will you

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1 recommend that we do about even that list? I mean,  
2 should we do more studies on it, should we have --

3 DR. BRATER: I would.

4 DR. KONSTAM: But if we were to approve  
5 the drug, if the drug were to get approved, what would  
6 you be saying about that list of drugs right now?

7 DR. BRATER: Well, I think again you can  
8 take two approaches. One would be to say it is highly  
9 likely that the Cimetidine effect is the biggest that  
10 you are going to see, so you could basically say, we  
11 are just going to assume that all those other things  
12 maybe have the same magnitude of effect as Cimetidine,  
13 and just lump them all together, and label  
14 accordingly.

15 Or one could go back and recommend some  
16 specific studies. And I'm sure that is why that is a  
17 specific question that the Agency is going to ask you  
18 to address.

19 DR. KONSTAM: Just one last thing. Oral  
20 contraceptives, I came across something in the data  
21 that there is an interaction. And I didn't hear you,  
22 really, talk about it in any way.

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1 DR. BRATER: Yes, I think that is worth  
2 actually spending a minute on. Let me first how you  
3 the data that triggered that question, backup slide  
4 52.

5 And this is a study that was not designed  
6 to address the effect of oral contraceptives on  
7 Dofetilide, it was the converse. In effect to see,  
8 does Dofetilide affect oral contraceptives.

9 But Dofetilide concentrations were  
10 obtained, and lo and behold the seam axis were quite  
11 high, even relative to this larger dose. So then the  
12 question was raised, my goodness, do orally  
13 contraceptives potentially inhibit the metabolism of  
14 Dofetilide.

15 To try to get a handle on that, the first  
16 step was to go back and look at the phase 1 studies in  
17 the U.S. and essentially merge data and look at women  
18 on oral contraceptives, as opposed to not on oral  
19 contraceptives. And those data are in backup 50.

20 And, again, this is basically a  
21 retrospective analysis, taking data from individual  
22 study reports. And so here women on no oral

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1       contraceptives, females on oral contraceptives, if you  
2       look at AUCs, they are pretty much the same in the  
3       seam axis. So they don't look nearly like what was  
4       seen before.

5               Now, so that then raises several  
6       questions. Why were those Dofetilide concentrations  
7       as high as they were? One thing, and if you want me  
8       to show you the data I will. The assay, the quality  
9       controls on Dofetilide assay were running abnormally  
10      high that day, with that run, about 18 percent high,  
11      so there could be an assay thing.

12             But I think most importantly this  
13      stimulated a study to specifically address the  
14      question. A little bit variation of the theme, and  
15      that was hormone replacement therapy in elderly  
16      patients.

17             And I can show you some preliminary data  
18      in that, in 12 of the patients that have been  
19      analyzed. So let me show you that, that is backup  
20      slide 45.

21             So this is single dose. Again, in equal  
22      12, emphasizes the preliminary data. The end is going

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1 to be about -- this is about two-thirds of the  
2 patients. And you see this little shoulder here, but  
3 otherwise basically the plasma concentrations are  
4 quite comparable.

5 The next slide, which is backup 46, shows  
6 it at steady state. That was single dose, here is at  
7 steady state. And the area in the curves here are  
8 really quite similar.

9 So there doesn't seem to be an effect of  
10 hormone replacement therapy. And, parenthetically,  
11 you wouldn't expect one. If you look at -- let me see  
12 backup 39. If you look at in vitro studies, and you  
13 look at the ability of ethinylestradiol to affect  
14 metabolism of Dofetilide, which is on this axis, you  
15 see, you have to get way over here before you start  
16 seeing an effect.

17 Well, circulating Ethinylestradiol  
18 concentrations are basically back here at the Y Axis.  
19 So from in vitro data one would not predict an  
20 interaction, and the HRT data, that was a study  
21 specifically designed to address the issue.

22 And so I think those are probably the most

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1 definitive that we have on that question.

2 DR. ATKINSON: One comment on your slide,  
3 Craig, that you showed. Although the total area in  
4 the curve between the HRT and the controls wasn't  
5 perhaps significantly different, it did appear that  
6 the peak levels were higher in individuals getting  
7 HRT.

8 Now, do you ascribe that to an increase in  
9 blood flow getting back to the same mechanism that  
10 you've used for verapamil, or not?

11 DR. BRATER: Well, it could be from maybe  
12 some slight change in volume of distribution. If you  
13 look at C peaks, at least in the preliminary data,  
14 again, those -- there aren't any statistically  
15 significant differences.

16 But, again, the end is only about two  
17 thirds of what it is going to be.

18 DR. ATKINSON: Also, in terms of gender,  
19 there does seem to be a difference in the response of  
20 males and females to the Ketoconazole interaction, and  
21 it appears to me that the non-renal clearance in  
22 females is impaired, to a greater extent, by



1 Ketoconazole than in males.

2 DR. BRATER: Yes, I think that the data  
3 from the Ketoconazole study would indicate that the  
4 non-renal component of elimination in women, in that  
5 study, is about 40 percent, and that the Ketoconazole  
6 effect is to decrease that by, and my recollection is  
7 the number is 53 percent, so basically cut it in half,  
8 which would mean that in that group, if you are just  
9 looking at that group, your effect on total clearance  
10 is a decrease of 20 percent.

11 That is going to extrapolate, it is an  
12 inverse relationship. That would extrapolate to a  
13 change in the area under the curve of maybe 25 to 30  
14 percent.

15 ACTING CHAIRMAN CALIFF: Dr. Graboys?

16 DR. GRABOYS: I know you want to move  
17 along, but I want to ask the sponsors, they have to  
18 really help us out here, in terms of how to manage  
19 patients with this drug chronically. I mean, I think  
20 it is a horrendous problem right now.

21 First of all, in terms of the QT, I don't  
22 know what to make of the QT data when you have

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1 patients in atrial fibrillation with varying cycle  
2 lengths, and you are telling them to measure ten  
3 beats, and then make a judgement on the QT on that  
4 basis.

5 Other problems with the QT we have  
6 patients who are on 1A drugs, who on quinidine will  
7 display their QT way out, and never have a problem,  
8 and those with minimal changes will have a problem,  
9 and then you look at Amiodarone, in which you may see  
10 the longest QT, and nothing ever happens with those  
11 folks.

12 So the QT issue is, from my point of view,  
13 in a hospitalized patients a real problem.

14 Secondly, and as the point has been made,  
15 no one is going to be looking at creatinine clearance.  
16 And what happens when the patient is discharged from  
17 the hospital and now you want to increase the dose?  
18 Are you going to bring him back into the hospital?

19 So all of these -- I mean, you are going  
20 to have to be a rocket science to figure out how to  
21 orchestrate management of these patients. But the way  
22 the current suggestions are simply doesn't appear to

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1 me to be satisfactory.

2 ACTING CHAIRMAN CALIFF: I think, again,  
3 that is going to get to the clinical portion, and we  
4 have a lot of time devoted to that.

5 DR. THADANI: Yes. One comment, and a  
6 short question, I will try to restrict myself. I  
7 thought I was smart enough, and try to remember  
8 creatinine clearance on the one out of two studies,  
9 which I memorized, and on the tenth patient I forgot,  
10 and I couldn't convert kilograms into pounds.

11 So I think it seems easy, and yet I can  
12 assure you, when I'm standing in the unit nobody does  
13 it. It seems very simple, I think it can work  
14 toxicity is more complicated than you think. Now I  
15 can tell you 140 minus A multiply it, then you have to  
16 correct for the females .85, so it is easy, but it is  
17 difficult.

18 Now the -- when I'm treating Afib a lot of  
19 the patients are rapid rates, even if they are in  
20 chronic, and a lot of them are going to be. And as in  
21 the suggestion, we now talk about Diamond study, which  
22 is probably dysfunctional. A lot of them have a good

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1 LB function.

2 And they are either on Verapamil, or  
3 Diltiazem to control their rates. And Verapamil is a  
4 major issue of interaction here. And if you are going  
5 to give doses above 500 micrograms you run into  
6 trouble.

7 So does one have to stop Verapamil while  
8 you are worried about the rate, and watch the patient  
9 3 days, he is having palpitations?

10 And the other question is, what about any  
11 interaction between Diltiazem, because you showed in  
12 L-Dopamine there is no interaction, but Diltiazem you  
13 did not show any pharmacokinetic, or pharmacodynamic  
14 data.

15 And the last one is related to your over  
16 the counter antihistamines, which are also -- can  
17 cause Torsade, and I know it will come in the  
18 protocol. They were excluded. Have you looked at any  
19 interaction, either on the QT or just your  
20 pharmacokinetics?

21 DR. BRATER: In terms of the Verapamil  
22 question, I mean, Verapamil should contraindicate a

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1 patient having the drug. So then by definition that  
2 would mean if you wanted to use Dofetilide you would  
3 have to stop Verapamil and get them well adjusted and  
4 get --

5 DR. THADANI: For how long? Some of them  
6 are once a day 240, 320, long acting. So you suggest  
7 to stop it for two days, one day, and then start your  
8 drug, prolong hospitalization for another day, or  
9 what?

10 DR. BRATER: Well, the half life of  
11 Verapamil is pretty short. The sustained release  
12 preparations mean that it persists for a while, but as  
13 soon as you stop it goes away quickly. So you don't  
14 have to have them off for a prolonged period of time  
15 before you did that.

16 DR. THADANI: So you recommend another day  
17 before you start, if you were to approve to start this  
18 drug?

19 DR. BRATER: Well, I don't remember the  
20 half life of Verapamil, but my recollection is that a  
21 day would be certainly four times a half life, and  
22 that ought to be enough, unless there is something in

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1 the patient that prolongs the half life.

2 You would have to look, I mean that --

3 DR. THADANI: So none of the patients were  
4 given the drug in question on top of Verapamil in the  
5 studies, am I right?

6 DR. BRATER: I'm sorry?

7 DR. THADANI: So that you have to stop the  
8 drug before you actually give them the first dose,  
9 that is what you are saying?

10 DR. BRATER: Yes, I would worry about the  
11 magnitude of this effect. I would -- yes.

12 DR. THADANI: What about Diltiazem, is  
13 there any --

14 DR. BRATER: Diltiazem there are no data,  
15 and I think if another study is done to probe that  
16 issue, that would be a logical one to do.

17 DR. THADANI: And the reason I'm asking is  
18 because is because Diltiazem is used pretty often than  
19 you think, you know, patients are on Digoxin, I'm  
20 talking about relatively good function, we see also  
21 post-op patients that come on IV Diltiazem.

22 DR. BRATER: I think you said there is no

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1 data.

2 DR. THADANI: So are you suggesting we  
3 should do a fairly large study to look at that?

4 DR. BRATER: Well, I'm not so sure it has  
5 -- I think the first cut would be to basically do a  
6 very rigid interventional trial, in a tightly  
7 controlled group of patients to see, and then that  
8 would drive whether or not you needed a very large  
9 study after that. That could be readily addressed.

10 ACTING CHAIRMAN CALIFF: Bob?

11 DR. TEMPLE: I think this is right.  
12 Verapamil's half life changes with time. So that by  
13 the time you've been on it for a few weeks it is  
14 probably more than half a day.

15 DR. BRATER: Okay, then they need to be  
16 off two days.

17 DR. TEMPLE: Right. What is the half life  
18 of Dofetilide? I thought there was a reference to 20  
19 some odd hours, but the other data I've seen here, in  
20 one of your slides says it is closer to seven. So --

21 DR. BRATER: Yes, seven, ten, somewhere in  
22 that range. And people with decreased renal function

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1 down to like 20 mills per minute, it is about 22.

2 DR. TEMPLE: Okay, then it gets longer.  
3 Is the Verapamil data, at least for the AUC, a  
4 reasonable test of drugs with intermediate levels of  
5 3A4 inhibition, or do you actually think you have to  
6 go and look at erythromycin and things like that?

7 DR. BRATER: Well, see, I don't think you  
8 know because Verapamil probably also inhibits P-  
9 glycoprotein. So is it a renal-- would it be a renal  
10 secretory effect, or a metabolic effect.

11 And, so, you would have to again do some  
12 more specifically targeted studies to tease that out.

13 DR. TEMPLE: I guess you could form the  
14 impression, from all of this, that there is so many  
15 different things showing up. I mean, with alteration  
16 of renal function, as well as possible 3A4 effects, at  
17 least in people with diminished renal function, early  
18 versus late, that it is hard to conclude anything  
19 without actually looking at it?

20 DR. BRATER: Well, I guess if you are  
21 saying there are some specific, at least in my domain,  
22 of drug interaction stuff, are there a few specific

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1 studies that would offer additional information that  
2 might be helpful? I don't think there is any question  
3 about that.

4 DR. TEMPLE: I guess I was struck by the  
5 Verapamil data, where you think you are doing okay,  
6 because it doesn't do much through its 3A4 inhibition,  
7 and then sort of unexpectedly you get a 50 percent  
8 increase in C-max, which is probably the thing you are  
9 worried about more.

10 DR. LIPICKY: I have gotten confused as  
11 this discussion went on, and just want to return to  
12 the population pharmacokinetic study. And you said  
13 when you dropped the Ketoconazole plasma concentration  
14 data into that data base pool, that that signal that  
15 came from Ketoconazole was fairly well obvious, and  
16 was able to be picked out.

17 How many other signals, one, two, three,  
18 four, were picked out of that pharmacokinetic screen,  
19 and how many different drugs were people on during the  
20 course of the trials, did you ever say that?

21 DR. BRATER: I said, as I went through, in  
22 terms of groups of drugs, and that are 3A substrates,

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1 3A inhibitors, P-glycoprotein, potential P-  
2 glycoprotein inhibitors, cation, substrates, cation  
3 inhibitors, I enumerated those values as I went  
4 through those parts of the presentation.

5 DR. LIPICKY: Pretty many?

6 DR. BRATER: In the hundreds. Well, it  
7 depends, on the cation, cationic inhibitors it was 20.

8 DR. LIPICKY: 20?

9 DR. BRATER: But there was a -- there was  
10 a -- it depends on how you define it. That analysis  
11 suggested a 14.6 percent decrease in clearance with  
12 those. Is that clinically significant or not? It  
13 depends on how you define that.

14 DR. LIPICKY: Well, I understand, but the  
15 thing is that in fact you could identify drugs that  
16 had some of those properties, and they were fairly  
17 large numbers, and you could actually identify that  
18 there was an effect, and sort of have a feeling for  
19 what its magnitude is, and how worried you need to be  
20 about it.

21 DR. BRATER: Right.

22 DR. LIPICKY: And you want to leave it

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1 from the vantage point of would the biggest sort of  
2 population kinetic change you saw was in the 10 to 15  
3 percent range?

4 DR. BRATER: Well, when we put these  
5 Ketoconazole data in there it was -- I think it was 33  
6 percent.

7 DR. LIPICKY: And that was the biggest  
8 thing you saw?

9 DR. BRATER: Right.

10 DR. LIPICKY: So is that a reasonable  
11 characterization of that stuff? I mean, if I were to  
12 say that from the population kinetic data base the  
13 worst actor that was seen in a definitive drug  
14 interaction study that changed things by 35 percent,  
15 that just popped out like a sore thumb, and that other  
16 drugs you would expect to do something, in fact were  
17 identifiable, but the changes were in the order of ten  
18 percent, and that although all of this is important to  
19 think about studying more, because there is lots to  
20 learn, that is what academics like to do.

21 Would I be improperly characterizing the  
22 circumstance?

1 DR. BRATER: I guess it really depends a  
2 lot on, you know, would you want to put all your money  
3 on -- invest all your money in the bank of the  
4 population analysis is what you are asking, really.

5 DR. LIPICKY: And I know you don't like  
6 population analysis, but it seems to me that there is  
7 -- that some of the questions that people have been  
8 asking are in there.

9 DR. BRATER: Right.

10 DR. LIPICKY: And it is not like this is  
11 totally unknown and at sea. It might be that you  
12 wouldn't want to put all of your money on that, but in  
13 fact there is something there, and some people would  
14 put some of their money on that.

15 DR. BRATER: Right. Well, I can show you  
16 the data, if you want to, it is backup slide 29.

17 DR. LIPICKY: That would be nice.

18 ACTING CHAIRMAN CALIFF: Dr. Ryder wants  
19 to make a comment, I think.

20 DR. RYDER: I just want to be sure that  
21 there was an addendum to the briefing document that  
22 covered the population pharmacokinetics, and it has a

1 lot of tables, and lists of medications, including  
2 Diltiazem, including Verapamil, and the hundreds of  
3 patients that were on different medications, because  
4 one of the -- one of the items that I would like to  
5 point out is that it is a very large data set, and the  
6 population PK and the pharmacodynamics of that, the  
7 QTc change, and as Dr. Pratt will get into later, the  
8 various safety cuts were looked at, according to the  
9 concomitant medication.

10 I just want to make sure that the  
11 Committee had the addendum.

12 ACTING CHAIRMAN CALIFF: Thank you, I  
13 think that is -- we did get the addendum, and it is  
14 helpful. I agree with the sentiment of several people  
15 that we should go ahead and look at that data, then.

16 DR. BRATER: And what I'm going to show  
17 you is the PK data. In the supplement that was  
18 described there is also an extensive analysis of  
19 population Torsade relationship and mortality. It is  
20 backup slide 29.

21 So here is the peak inhibitors, a cationic  
22 transport. So an N of 20, in first visit, and this is

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1 a signal of 14.6 percent. And you see the ends on  
2 some of these are pretty healthy, okay?

3 The only other one that really pops up is  
4 Thiazides.

5 ACTING CHAIRMAN CALIFF: Craig, just  
6 because we haven't seen much of this kind of data, in  
7 this panel recently, could you just describe how the  
8 study was done?

9 DR. BRATER: Well, this is basically,  
10 again, this is a data base with these 1,445 patients,  
11 and throughout the course of their therapy they had  
12 serum sampling at different times, a total of about  
13 10,000 samples.

14 And then what you can do from that is you  
15 can estimate the pharmacokinetics using non-linear  
16 mixed effects modeling. You can estimate the  
17 pharmacokinetics on each one of those patients, and  
18 then you can do essentially a multivariate analysis and  
19 see how other things going on in that patient, be it  
20 demographics, concomitant disease, or concomitant  
21 medications affect the different pharmacokinetic  
22 parameters.

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1           So this is concomitant meds, and here is  
2           the signal that was picked up in terms of effects on  
3           clearance.

4           Why Thiazides might jump out, I don't  
5           know. But that might warrant further study as, Ray,  
6           you are basically saying, maybe this kind of targets  
7           you down where you are going to do those additional  
8           studies.

9           ACTING CHAIRMAN CALIFF:       Were the  
10          concentrations drawn in a particular relationship to  
11          the dose?

12          DR. BRATER: No, actually, what you want  
13          in these kind of studies is you want to have -- you  
14          don't want things drawn consistently at a time in  
15          relationship with the dose. You want to know when the  
16          dose was given, and when the sample was drawn, but you  
17          want that to be different at different times, and that  
18          is how you use this technique to then go back and  
19          construct the individual patient's PK.

20          DR. KOWEY: I'm Peter, over here. This  
21          sort of runs both ways, and I think it is going to be  
22          very important for Craig to spend some time on this,

1 because one of the things that really stood out in  
2 this analysis, this addendum, was the Digoxin, and the  
3 fact that there was a higher risk of Torsade with  
4 concomitant Digoxin use, despite the fact that it  
5 didn't show up as an interaction.

6 DR. BRATER: Yes, so what that says is  
7 that that is not a kinetic interaction.

8 DR. KOWEY: I know that. I'm saying, that  
9 is exactly right, that is exactly my point. It did  
10 not show up as a kinetic interaction, and yet in the  
11 population study -- maybe the reason you don't like  
12 population studies, and I don't like them either, is  
13 because it doesn't have any precision.

14 And one of the problems with precision is  
15 explaining interactions which are maybe not PK  
16 interactions. Obviously that has to be some kind of  
17 pharmacodynamic interaction, if it is true.

18 But one of the -- it does work both ways.  
19 I mean, you can use these things for some comfort, but  
20 it also raises a little bit of anxiety in my mind,  
21 because now we have an interaction that we weren't  
22 supposed to have on a real true endpoint, which is

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1 Torsade.

2 So we have to deal with that somehow, and  
3 maybe that will come up in Craig's presentation.

4 DR. KONSTAM: If you could clarify, if you  
5 look at, for example, thiazide diuretics, minus 16  
6 percent, but we don't know whether that is not being  
7 driven by one particular thiazide diuretic that has  
8 particular drug/drug interaction that may or may not  
9 be characteristic of all thiazide diuretics.

10 So there could be something hiding in  
11 there. Well, I guess I will ask the question,  
12 couldn't there be something hiding in there that has  
13 a dramatic effect, and so therefore, how reassured am  
14 I that because 95 patients were on thiazides, but  
15 maybe 10 of them were on a certain drug? We don't  
16 know.

17 DR. BRATER: No way to sort that out.

18 ACTING CHAIRMAN CALIFF: I want to  
19 register a difference of opinion with Peter. I love  
20 these studies because they are less precise, but they  
21 do reflect what actually happens to patients. And  
22 although there are problems with them, there is more

1 to interactions than just the kinetics.

2 DR. KONSTAM: I agree. And that is why I  
3 don't -- I'm not going to ask Craig to do it now, but  
4 he is going to have to do it to look at the other  
5 aspect of this, which is the pharmacodynamics, and  
6 true effects, not just focusing on the PK data.

7 I agree with you Rob. I think the part I  
8 don't like is this part. The whole global picture is  
9 actually very helpful.

10 ACTING CHAIRMAN CALIFF: Well, we have  
11 both FDA representatives I guess Bob, you are next,  
12 and then Ray.

13 DR. TEMPLE: I think there is a lot of  
14 reason to like these analysis, too, apart from the  
15 fact that they touch on far more things than you can  
16 reasonably be expected to study intimately.

17 They give you numbers that small studies  
18 often don't, even if you don't have as much precision.

19 Is there some reason not to think that  
20 thiazides are just working by decreasing creatinine  
21 clearance? I mean, they do that a little.

22 DR. BRATER: I mean that would be my first

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1 hypothesis, that that is the logical thing that would  
2 happen. But I think what you are leading to is that  
3 these kind of data lead to hypothesis generation, that  
4 will lead you to that next step.

5 DR. TEMPLE: Yes, that is commonly said.  
6 I'm not sure these aren't just as believable as the  
7 typical small interaction studies we see. There are  
8 some examples that suggest that sometimes you get  
9 better data from these.

10 But these could certainly be looked at  
11 individual diuretics, if you wanted to. You would  
12 reduce your number, but someone could certainly do  
13 that if that was of interest.

14 And a lot of the effects are the ones you  
15 would expect. 3A4 inhibition gives you a sort of  
16 minor effect, just what you would imagine with only 20  
17 percent of the clearance being due to that.

18 So there is a certain -- I like these  
19 things. The other point that I guess you were making  
20 is, this is a pharmacokinetic analysis, it is not  
21 supposed to predict that Digoxin has a pharmacodynamic  
22 interaction, that is another problem, that is why you

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1 look at what people are on when they get their  
2 Torsade.

3 ACTING CHAIRMAN CALIFF: Ray?

4 DR. LIPICKY: I just want to echo what Bob  
5 just said, in that it isn't a matter of like or  
6 unlike. I think I object to the word of imprecise.  
7 You know, I don't know what that word means.

8 The point, I think, and it is right there  
9 on the slide, is that with observational data, and  
10 that is what you get when you grab a blood sample, and  
11 you write down what time the drug was given, and when  
12 the drug sample was gotten.

13 And that you get the drug sample, any  
14 time, at midnight, or at 2 a.m., or at 12 o'clock  
15 noon. And you dump it into something that can do  
16 something with that kind of data, you really can  
17 distinguish stuff.

18 That is not imprecise to me. It will only  
19 find stuff in relationship to plasma concentrations.  
20 It isn't going to find stuff in relationship to  
21 others, although it will, if you plug other  
22 information in.

1           So it isn't a matter of precision, but it  
2           is a matter of hypothesis generation. That is, you  
3           know, you don't know exactly what is going on, you --  
4           it identifies signals that might require greater  
5           study, but the thing that is missing from here is the  
6           Ketoconazole guide.

7           That is the guide that the last study that  
8           was done, and it is sort of the biggest  
9           pharmacokinetic interaction. That resulted in a 43  
10          percent change in clearance. That is a very big  
11          number compared to any of these other numbers that are  
12          there.

13          And the only reason I think we are looking  
14          at these, is these are mean changes, obviously, and  
15          some of the people had big changes, and some people  
16          had little changes.

17          The only reason for looking at this is  
18          this gives a feeling for magnitude. How big a problem  
19          is this. And on average it is in the 10 to 15 percent  
20          range in plasma concentrations.

21          Now, that has to be put into the equation  
22          with what the relationship between plasma

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1 concentration and QT is, and what one knows about the  
2 relationship between QT and Torsade, which we will get  
3 to.

4 But I wouldn't want to leave this in an  
5 imprecise term. I think that is bad, just, semantics.

6 ACTING CHAIRMAN CALIFF: Joan, do you have  
7 another question?

8 DR. LINDENFELD: Just quickly. Can we  
9 assume that these changes in clearances are additive,  
10 as you add on drugs; is that a fair assumption?

11 DR. BRATER: No.

12 ACTING CHAIRMAN CALIFF: You took the  
13 question I was going to ask, which gets to an  
14 analytical issue which I don't think was presented in  
15 the packet.

16 Another thing that this type of analysis  
17 should allow you to do is to look at combinations. It  
18 is essentially a multivariable problem. And we know  
19 that since this is going to be an elderly population,  
20 most of them are on multiple medications.

21 And one reason I like this kind of study  
22 is that your typical 24 patient study of interaction

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1 is looking at one thing at a time, whereas here you  
2 have the opportunity to see if combinations of drugs  
3 are additive, multiplicative.

4 Was this looked at?

5 DR. BRATER: Well, I think whether or not  
6 they are additive or multiplicative is probably going  
7 to depend on the pathway that they are affecting. So,  
8 for example, if you had a drug that had Ketoconazole  
9 like effect on the metabolic component, and then you  
10 added another drug that affected only the cationic  
11 secretory component, then those are going to be  
12 additive, no question about it.

13 But if you put two organic cation  
14 inhibitors in a patient, as opposed to one, will it  
15 be? It is, you know, it may be -- it is going to  
16 depend on the doses, it is going to be dependent upon  
17 the intrinsic activity of each of those towards  
18 affecting that pathway, etcetera.

19 ACTING CHAIRMAN CALIFF: But it wasn't  
20 looked at as to whether, for example, if one was on  
21 nitrates and thiazides, there was a minus 25 percent,  
22 or a minus 50 percent?

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1 DR. BRATER: No, but that ought to be able  
2 to be done.

3 ACTING CHAIRMAN CALIFF: Okay. I had  
4 three or four questions. If we could just put back up  
5 the slide that says QTc efficacy relationship by dose?

6 DR. BRATER: That is core slide, I think  
7 it is 21.

8 ACTING CHAIRMAN CALIFF: The first  
9 question is if you -- and I think this is really a  
10 key, at least from my perspective, is a key plot. If  
11 you plotted probability of Torsade alongside the  
12 probability of remaining in normal sinus rhythm, would  
13 the slope be exactly the same as the normal sinus  
14 rhythm plot, or would it be deviant from that?

15 DR. BRATER: I'm not -- well, I think you  
16 would have to -- if you took each, I don't know if you  
17 can do that. I mean, the numbers are so small. It is  
18 what I've been told. I mean, I asked people to do  
19 that, and they told me the numbers are so small you  
20 can't do that.

21 ACTING CHAIRMAN CALIFF: Well, if we don't  
22 look at the numbers then we are left with having to

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1 just guess about it. I would think at least seeing  
2 the data would be better than -- and I guess maybe we  
3 will.

4 DR. BRATER: Well, I know that -- I don't  
5 know if it is out in other pieces of the data that are  
6 coming forward, but --

7 ACTING CHAIRMAN CALIFF: I mean, there is  
8 a plot in our briefing booklet about the probability  
9 of Torsade as a function of QT. So it seems like we  
10 could do it by trying to put one on top of the other  
11 in our briefing books, but it would be nice if there  
12 was some way to get a more definitive picture.

13 DR. BRATER: I don't know who has that  
14 slide. Is that yours, Craig?

15 ACTING CHAIRMAN CALIFF: Well, maybe that  
16 is something we can come back to when you have a  
17 chance to think about it.

18 The second question is, do we know what  
19 the same slide would look like for Quinidine, or  
20 Amiodarone?

21 DR. BRATER: I'm not the expert, Ray is  
22 the expert, he says no.

1 DR. LIPICKY: From my point of view, I  
2 will say absolutely not, not the slightest perception.

3 ACTING CHAIRMAN CALIFF: Dr. Atkinson?

4 DR. ATKINSON: I think an essential  
5 assumption here is, is QT interval prolongation a  
6 reliable surrogate for Torsade? And I don't know, I  
7 would like to pool maybe other members of the  
8 committee here, but my impression is that I have to at  
9 least see some patients who have had minimal QT  
10 prolongation at a time when they've had Torsade.

11 And so even though both QT interval and  
12 risk of Torsade may increase with increasing blood  
13 level, and I'm not sure that QT prolongation  
14 necessarily lies on the causal path to Torsade.

15 DR. LIPICKY: We could spend three days  
16 talking about this, and so my summary statement that  
17 I will make, from my vantage point is, summarizing  
18 three day's worth of debate, and I have absolutely no  
19 data, whatsoever, to support the statement I'm going  
20 to make.

21 The QT interval, any drug that has caused  
22 an increase in QT interval, has also caused Torsade.

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1 Torsade occurs in the absence of a drug that causes  
2 increases in QT. Torsade probably occurs in the  
3 absence of an increase in QT, although you can't make  
4 the diagnosis, because you can't call Torsade,  
5 Torsade, unless you have an increased QT.

6 But people certainly see multiform  
7 ventricular tachycardia, which is what Torsade de  
8 points is, plus a long QT somewhere identifiable  
9 before you see the episode.

10 So the thing that makes it Torsade is  
11 seeing the QT somewhere. And if you don't see a QT  
12 somewhere, you call it multiform ventricular  
13 tachycardia. I don't know that those are different,  
14 all right?

15 So if you believe Torsade is a special  
16 entity, then indeed it doesn't occur without a long  
17 QT. But if you think Torsade is just a certain thing  
18 that happens, then it could be multiform detach, you  
19 don't need a long QT.

20 So that is point number one. Point number  
21 two is that at doses that -- at plasma concentrations  
22 that give you longer QTs, on average, you have a

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1 greater incidence of Torsade on average, and that  
2 certainly is true.

3 But that -- but the incidence of Torsade  
4 in people that have long QTs, like people who have  
5 long QT syndrome, is an incident -- their QT is long  
6 all the time, is they have Torsade once every five  
7 years. But every bloody beat for those five years has  
8 a long QT.

9 So it isn't the long QT, it is something  
10 else. But the long QT is associated with whatever it  
11 is. And we can talk about this for three days, and  
12 not get to an answer.

13 And that is my summary of three day's of  
14 debate.

15 ACTING CHAIRMAN CALIFF: You just said  
16 that life is multivaried, and I think you and Dr.  
17 Atkinson probably agree. Bob?

18 DR. TEMPLE: I don't want to add to three  
19 days, either. The fact seems to be, though, that the  
20 mechanism of this class of antiarrhythmic and its  
21 benefit comes, at least partly, because it delays  
22 repolarization.

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1           So you are never going to have  
2 effectiveness without some effect on that. What isn't  
3 completely clear, however, since QT intervals vary  
4 throughout the day, is whether when you are looking at  
5 a drug that causes an average change, the problem  
6 really arises, for the small fraction of people that  
7 spend a little time over 500, and you just -- there  
8 isn't any way to really know that.

9           So here they have tried to exclude anybody  
10 who has a really robust increase, and maybe that is  
11 why you don't see so many cases. If you hadn't done  
12 that, and just had an average increase with a fraction  
13 of people going over 500 you might have more trouble.

14           So there is, as Ray says, I don't think  
15 there is any doubt that the two are related, but what  
16 exactly triggers it isn't clear, and it seems modestly  
17 clear that things like hypokalemia can make the same  
18 QT interval dangerous when it wasn't -- when it wasn't  
19 before.

20           But the implication here, I think, that is  
21 important is that you are not going to get  
22 effectiveness without some increase, and you have to

1 look at the rest of the data to see how dangerous that  
2 increase was, and how variable it is going to be with  
3 all these attempts to minimize extreme values.

4 I don't think there is any doubt, either,  
5 that a value over 500 is more trouble than a value of  
6 440.

7 ACTING CHAIRMAN CALIFF: I have one final  
8 question, and then we will take a break, which looks  
9 to me like it is sorely needed for some Gatorade, or  
10 something.

11 And this, again, is a relative question  
12 compared to other alternatives for these patients. If  
13 you look at the interactions that we've just gone  
14 through, would you say that these are more complex, or  
15 less well characterized, either one, than what we know  
16 about Quinidine and Amiodarone, and Sotalol for these  
17 patients, and the drug interactions, and their  
18 consequences on QT interval, or Torsade?

19 DR. BRATER: Well, again, Ray may be in a  
20 better position to answer that than I. It seems to  
21 me we know a lot more about this drug in terms of its  
22 PK than we do most others.

1           And that is in part, in my own mind, a  
2           function of this big population data base that was  
3           gathered that is impressively entirely consistent with  
4           what is seen in the shorter term studies.

5           So I think from a pharmacokinetic point of  
6           view that probably more is known about this than most  
7           that I've seen.

8           ACTING CHAIRMAN CALIFF: Dr. Atkinson, you  
9           are saying a lot of these -- and it is a two part  
10          question, one is the characterization itself, and the  
11          second is, looking at the characterization, is the use  
12          of this drug, with its interactions you think more  
13          complex than say, Quinidine or Amiodarone?

14          DR. ATKINSON: Well, one disadvantage,  
15          obviously, is that it hasn't been in the marketplace  
16          as long as other agents, so we really don't know. But  
17          I would say that the company has done an elegant job.

18          I particularly think that the PK,  
19          population PK study is extremely well done. And for  
20          those of you that wonder whether population PK studies  
21          always turn up the important signals I will tell you  
22          that Lou Shiner's first study on population PK of

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1 Digoxin completely missed the fact that Quinidine, on  
2 average, doubles Digoxin levels.

3 So that the ability to pick up the  
4 Ketoconazole signal here I think is most impressive,  
5 as a positive control.

6 I think there are holes in the sponsor's  
7 package, and I think Dr. Brater has certainly  
8 suggested some that might be corrected. But I would  
9 say that we know a lot more about this drug than  
10 Amiodarone.

11 I would say with regard to Quinidine that  
12 there have been a number of, you know, that drug was  
13 approved long before we had ever dreamed of population  
14 PK studies. I don't know of anything on Quinidine  
15 that could approach the kind of study that has been  
16 done here.

17 There have been ad hoc studies by academic  
18 investigators on Quinidine, but nobody has really done  
19 detailed interaction studies across the whole gamut of  
20 drugs that patients are on.

21 DR. KOWEY: I think Art is right, I think  
22 we do know more about this drug than we know about any

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1 other, and maybe I can defend a term that I used  
2 earlier about precision rate.

3 But one of the reasons why I'm concerned  
4 about that kind of an analysis is because we have  
5 never seen a drug, at least had a drug considered for  
6 approval for atrial fibrillation, which is not  
7 necessarily a lethal disease, in which the upper end  
8 of the dose of the drug is abutting so closely to a  
9 toxic effect.

10 And, therefore, drug interactions have  
11 never in my mind, at least, for AF? We are -- I'm  
12 talking about Torsade -- I'm sorry?

13 DR. LIPICKY: Weren't you part of saying  
14 Flecainide should be approved?

15 DR. KOWEY: No, I'm talking about Torsade  
16 risk right -- I'm talking about --

17 DR. LIPICKY: Weren't you part of the  
18 panel that said Quinidine should be approved?

19 DR. KOWEY: Flecainide.

20 DR. LIPICKY: Quinidine for atrial  
21 fibrillation?

22 DR. KOWEY: Yes, that is right.

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1 DR. LIPICKY: You think that is different?

2 DR. KOWEY: No, but I don't think we have  
3 ever -- no, we are looking at pharmacokinetic data  
4 that we didn't look at for Quinidine, because we  
5 didn't have it.

6 DR. LIPICKY: No, that is correct, so you  
7 know a lot more about this guy, and you were ignorant  
8 for Quinidine?

9 DR. KOWEY: That is right.

10 DR. LIPICKY: Okay.

11 DR. KOWEY: Just because you were ignorant  
12 of one drug, and smarter about another one, doesn't  
13 mean you can't look at the data.

14 ACTING CHAIRMAN CALIFF: I think it is  
15 time for a break, but I would just point out, probably  
16 the most amazing statistic, in light of this  
17 calculation that I saw this morning was that Quinidine  
18 is still the most frequently prescribed drug for this  
19 indication. After all this time we still don't know  
20 any of this data about Quinidine.

21 It is break time, 15 minutes we will be  
22 back.

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1 (Whereupon, the above-entitled matter  
2 went off the record at 11:08 a.m. and  
3 went back on the record at 11:30 a.m.)

4 ACTING CHAIRMAN CALIFF: What I suggest  
5 that we do is we go straight through the efficacy and  
6 safety presentations without stopping, because they  
7 both deal with the body of clinical trial evidence,  
8 and if we ask questions about one, and then the other,  
9 we are going to go over the same trials again and  
10 again. Is that acceptable?

11 And then we will save the balance  
12 presentation at the end, until after we've discussed  
13 the body of the clinical trial evidence.

14 Let's get started.

15 DR. FRIEDRICH: Dr. Califf, Dr. Temple,  
16 Dr. Lipicky, Members of the Advisory Committee, ladies  
17 and gentlemen.

18 I will present evidence for the Dofetilide  
19 efficacy in the maintenance and conversion of atrial  
20 fibrillation and atrial flutter to normal sinus  
21 rhythm.

22 I will begin by reviewing maintenance of

1 sinus rhythm, then I'm going to present data on dose  
2 response, subpopulations, and secondary endpoints of  
3 symptomatic benefit and quality of life improvements.

4 Finally I will review the Dofetilide  
5 effect on conversion to normal sinus rhythm in  
6 patients with chronic atrial fibrillation/atrial  
7 flutter.

8 Throughout my talk I will use the term  
9 chronic atrial fibrillation in the sense, as it is  
10 defined by the term persistent atrial fibrillation.

11 The entire Dofetilide clinical program  
12 included nearly 8,500 patients, 6,800 in the oral  
13 program, and 1,700 on the IV program.

14 The support for the clinical efficacy of  
15 Dofetilide comes from the oral program. Specifically  
16 I will be discussing the results from studies of  
17 approximately 1,100 patients who were included in the  
18 chronic atrial fibrillation trials.

19 All of these trials were double blind and  
20 placebo controlled. Patients enrolled in other parts  
21 of the program, including over 3,000 patients from the  
22 Diamond mortality trials, are discussed at the safety

1 presentation by Dr. Pratt later this morning.

2 Entry into the trials was limited to those  
3 patients where document target arrhythmia, no excessive  
4 QT prolongation, AV block, or body cardia.

5 Patients were excluded if there was  
6 evidence of acute myocardial infarction, unstable  
7 angina, unstable congestive heart failure, reversible  
8 causes of the target arrhythmia, or history of  
9 polymorphic ventricular tachycardia associated with QT  
10 prolonging drugs.

11 In all clinical trials treatment with  
12 Dofetilide is always initiated in the hospital, under  
13 continuous electrocardiographic monitoring.  
14 Consistent with the primary renal excretion of  
15 Dofetilide, the dose of Dofetilide is adjusted  
16 downward, if renal function is compromised, in order  
17 to maintain equivalent serum levels.

18 After the initiation of therapy, the dose  
19 is further reduced if QT or QTc is excessively  
20 prolonged.

21 Here is an example of how the algorithm  
22 works. After assessing the EKG to exclude patients

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1 with prolonged baseline QTc or QT, creatinine  
2 clearance is then calculated using the Cokcroft-Gault  
3 formula.

4 Note, this only requires a routine  
5 measurement of serum creatinine, and covers other  
6 important factors like age, weight, and gender.

7 For example, a patient randomized to 500  
8 micro on BID with normal renal function receives 500  
9 micro on BID Dofetilide. While this dose would be  
10 reduced by half, to 250 micro on BID, if creatinine  
11 clearance was between 40 and 60 milliliter per minute.

12 Patients below 20 milliliters per minute  
13 were excluded from the trials.

14 Two to three hours after the first dose  
15 the QT or QTc will be checked again, and in case of a  
16 15 percent increase, or an increase beyond 500  
17 milliseconds, the dose would be reduced by half.

18 This dose reduction is needed in those few  
19 patients with increased sensitivity to the drug's QT  
20 prolonging effect.

21 These dosing principles were implemented  
22 at various time points during the development program,

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1 as shown on page 17, figure 2, in your briefing  
2 document.

3 However, more than 70 percent of patients  
4 in the atrial fibrillation, atrial flutter trials were  
5 randomized to 500 micron on BID were dosed according  
6 to the creatinine clearance algorithm.

7 Let me now turn to the clinical trials  
8 that provide evidence of efficacy in the maintenance  
9 of normal sinus rhythm in patients with chronic atrial  
10 fibrillation or flutter.

11 In the dose finding studies, 311 and 320,  
12 doses ranging from 250 micro on BID to 750 micro on  
13 BID were explored.

14 A positive dose response relationship was  
15 identified and this led to the design of the  
16 confirmatory efficacy studies 120 and 345.

17 Study 345 was a large clinical trial in  
18 671 patients which showed unequivocal efficacy of  
19 evidence of efficacy by meeting the pre-specified  
20 endpoint with high statistical significance.

21 The result of the second large study in  
22 atrial fibrillation or flutter, study 120, are

1 strongly supportive of the findings in study 345, as  
2 I will discuss shortly.

3 Please note that all chronic atrial  
4 fibrillation trials were designed to measure time to  
5 first recurrence of the target arrhythmia. Relapses  
6 beyond the first reoccurrence of chronic atrial  
7 fibrillation were not captured.

8 Studies 345 provides evidence of efficacy  
9 of Dofetilide in patients with atrial  
10 fibrillation/atrial flutter. This is a trial  
11 conducted at 79 centers that involved a total of 671  
12 patients with chronic atrial fibrillation or flutter  
13 of duration ranging from one week up to two years.

14 Study 345 is a twelve months randomized  
15 parallel group, double blind, placebo and active  
16 control study. The active comparator is Sotalol.

17 The primary analysis of the trial compares  
18 the efficacy of Dofetilide with a placebo in  
19 maintaining normal sinus rhythm once a patient is  
20 successfully converted.

21 Here is a design for study 345. During  
22 the running period of up to 14 days, where atrial



1 fibrillation or flutter is documented by  
2 electrocardiogram the patients are anticoagulated.  
3 Patients are hospitalized for the initiation of blind  
4 therapy and are closely monitored during this phase.

5 All patients are considered to be at  
6 steady state by day three. Patients who did not  
7 convert pharmacologically to normal sinus rhythm, up  
8 to one hour after the day three morning dose,  
9 underwent DC cardioversion.

10 Patients who did not convert to normal  
11 sinus rhythm were discontinued from the study at this  
12 time point. During the maintenance phase regular  
13 visits occurred.

14 Patients were randomized to one of five  
15 treatment groups, 500, 250, and 125 microgram BID  
16 Dofetilide, placebo, or Sotalol, 80 milligram BID.  
17 Calculated creatinine clearance was used to adjust  
18 doses downward.

19 The actual numbers of patients who  
20 received lower doses are shown on the bottom of the  
21 slide. For example, of the 129 patients who were  
22 randomized to 500 microgram BID, 96 received their

1 dose, and 33 were dose adjusted to achieve an  
2 equivalent serum exposure.

3 This is a predominantly male population,  
4 average age 65. About 50 percent of structural heart  
5 disease and approximately 45 percent have neurochord  
6 association function at less two or three.

7 Ninety percent of the patients have atrial  
8 fibrillation, ten percent have atrial flutter.  
9 Overall the mean duration of atrial fibrillation or  
10 flutter is 144 days. There are no clinically  
11 meaningful differences in the baseline characteristics  
12 between the Dofetilide and placebo treatment course.

13 The concomitant medications, Digoxin,  
14 diuretics, and ace inhibitors are typical of this  
15 patient population with mild to moderate concomitant  
16 cardiovascular disease. Use of concomitant medication  
17 was comparable between the treatment arms.

18 Let's now look at the pre-specified  
19 primary endpoint. Using point estimates from the  
20 Kaplan-Meier curves at 12 months, maintenance rate are  
21 66 percent, 51 percent, and 39 percent on Dofetilide,  
22 compared to 21 percent on placebo.

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1 Differences between Dofetilide and placebo  
2 at 12 months are highly statistically significant.

3 So the vastness of efficacy in this study  
4 is confirmed by an intention to treat analysis wherein  
5 patients that did not convert to normal sinus rhythm  
6 were included as treatment failures at the zero.

7 The initial drop in the Kaplan-Meier curve  
8 represents these patients. Retaining these patients  
9 in the analysis does not change the overall outcome of  
10 the trial.

11 Dofetilide in this analysis is more  
12 effective than placebo, and the dose response  
13 relationship is preserved with high statistical  
14 significance.

15 Study 120 examines the efficacy of  
16 Dofetilide in 325 patients with atrial fibrillation or  
17 flutter and is supportive of the findings in study  
18 345.

19 The primary endpoint of this trial is the  
20 proportion of patients in normal sinus rhythm as  
21 estimated by the Kaplan-Meier method. The primary  
22 analysis is the intention to treat comparison of the

1 maintenance of normal sinus rhythm among the four  
2 treatment groups at 6, 9, and 12 months, by the  
3 Locarin test, noting that the sample size estimate was  
4 based on the six month's time point.

5 This analysis is repeated for all data  
6 through to the 12 month study visit. Kaplan-Meier  
7 estimates for the proportion in normal sinus rhythm at  
8 6, 9, and 12 months are examined. The study design is  
9 similar to the design used in study 345.

10 Patients who are randomized to one of four  
11 treatment groups, 500, 250, 125 microgram BID  
12 Dofetilide or placebo. And the dose could be adjusted  
13 for both baseline creatinine clearance and QT  
14 prolongation.

15 The actual doses received, and patient  
16 numbers, are shown in the lower half of the slide.

17 The baseline characteristics for this  
18 population were similar to those of studies 345, with  
19 the exception of structural heart disease, which is  
20 more prevalent in study 120. The majority of patients  
21 are functional and record functional class 2 and 3.

22 In contrast to study 345, more patients in

1 this study are treated with Digoxin, 80 percent;  
2 diuretics, beta blockers and ace inhibitors.

3 These findings reflect the population with  
4 more advanced cardiovascular disease in this study,  
5 relative to studies 345.

6 The primary pre-specified analysis of this  
7 12 month study is the comparison of the proportion of  
8 patients maintaining sinus rhythm across the four  
9 treatment groups at 6, 9, and 12 months.

10 All randomized patients are included, with  
11 patients never achieving normal sinus rhythm  
12 considered treatment failures at times zero. This is  
13 represented by the initial drop in the Kaplan-Meier  
14 curve.

15 The curve show clear trend of increasing  
16 efficacy with increasing Dofetilide dose. The pre-  
17 specified overall Locarin test across treatment  
18 groups, up to six months, is non-significant, with a  
19 P value of .125.

20 Applying the identical test to all data  
21 from the start of the study through 12 months  
22 demonstrates a difference across all treatment groups

1 with a nominal P value of .035.

2 Not surprisingly, assuming linear dose  
3 response, and applying a statistical test for trend  
4 using nominal P value for 6 and 12 months, of .02, and  
5 .006, respectively.

6 At 12 months 47 percent of patients  
7 assigned to 500 microgram BID, and 20 percent of the  
8 placebo patients are in sinus rhythm. This difference  
9 has a nominal P value of .008.

10 A pre-specified secondary analysis of the  
11 maintenance population including only those patients  
12 converting to normal sinus rhythm is shown here. This  
13 is discussed in more detail on pages 50 to 52 in your  
14 briefing material.

15 This analysis is comparable to the primary  
16 analysis of studies 345. It shows 58 percent of  
17 patients assigned to 500 microgram BID in normal sinus  
18 rhythm at 12 months, compared to 25 percent on  
19 placebo. This difference has a nominal P value of  
20 .001.

21 To examine dose response we looked at the  
22 four atrial fibrillation trials. As shown here, we

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1 found a positive dose response relationship across all  
2 four clinical trials in chronic atrial fibrillation.

3 This was first demonstrated in the dose  
4 ranging studies 311 and 320, and subsequently  
5 confirmed in the large clinical trials 345 and 120.

6 Now I would like to discuss subpopulations  
7 and maintenance of normal sinus rhythm. This is best  
8 done by pooling two large trials, studies 325 and 120,  
9 into a combined atrial fibrillation or flutter data  
10 set.

11 The justification for this pooling is that  
12 both trials are similar in design, and as shown here,  
13 had similar results. For example, about 60 percent of  
14 patients remained in normal sinus rhythm on 500  
15 microgram BID in both trials at 12 months in the  
16 maintenance population.

17 The hazard ratios derived from this  
18 combined atrial fibrillation/atrial flutter data set,  
19 demonstrate reduced risk for relapse shown here for  
20 patients assigned to 500 microgram BID.

21 These data are discussed on page 54 to 56  
22 in your briefing material.

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1 Superior efficacy for Dofetilide, compared  
2 to placebo, in maintaining normal sinus rhythm in the  
3 following subgroups is demonstrated in patients with  
4 atrial fibrillation or atrial flutter, in males, or in  
5 females, or in patients below or above the age of 65.

6 We examined the effect of our dosing  
7 algorithm on efficacy in the maintenance of normal  
8 sinus rhythm in the same combined data set. The first  
9 group represents patients randomized to 500 microgram  
10 BID, whose dose is not adjusted.

11 The second group represents patients  
12 adjusted for creatinine clearance at baseline,  
13 compared to placebo patients.

14 While efficacy is estimated to be less  
15 than what is observed in unadjusted patients, it  
16 cannot be determined whether this is due to dose  
17 adjustment, or differences in the underlying patient  
18 characteristics of these two populations.

19 A hazard ratio cannot be determined for  
20 those few patients with dose adjustment for excessive  
21 QT or QTc prolongations, because a matching group of  
22 placebo patients predisposed to excessive QT or QTc

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1       prolongations cannot be identified.

2               These few patients are not shown here on  
3       the slide. However, I can tell you that nine of the  
4       thirteen patients in this group remained in normal  
5       sinus rhythm at 12 months.

6               Overall, of the patients randomized to 500  
7       microgram BID Dofetilide in studies 345 and 120, 72  
8       percent were treated according to the proposed  
9       treatment algorithm.

10              Let me summarize the results presented so  
11       far. Evidence for efficacy in the maintenance of  
12       normal sinus rhythm in chronic atrial fibrillation or  
13       flutter was demonstrated in a large double blind  
14       placebo control trial, with a pre-specified endpoint  
15       was reached with high statistical significance.

16              These findings were corroborated by  
17       another large placebo control trial, study 120, that  
18       was clearly supportive of efficacy at the 500  
19       microgram BID dose, with statistically significant  
20       nominal P values at 12 months.

21              Furthermore, a positive dose response  
22       relationship in the early dose ranging studies 311 and

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1 320 was confirmed in trial 345 and 120.

2 Finally, in a combined atrial  
3 fibrillation/atrial flutter data set efficacy was  
4 demonstrated when examined by arrhythmia type, gender,  
5 age, and renal function.

6 Pre-specified secondary endpoints in  
7 trials 345 and 120 included measures of quality of  
8 life and symptoms. Although not powered for this  
9 endpoint, analysis from these studies might provide  
10 some insight into the expected benefits of maintaining  
11 patients in normal sinus rhythm.

12 In studies 345, multiple validated  
13 instruments such as SF36, psychological well being and  
14 perception of symptoms were used to collect quality of  
15 life data.

16 In study 120 symptoms, severity, and  
17 frequency data were collected using symptoms  
18 previously established as relevant in patients with  
19 atrial fibrillation or flutter by the Duke group and  
20 others.

21 The analysis shown here is a percentage of  
22 patients with improvement from baseline symptoms

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1 across the eight quality of life instruments, by  
2 rhythm status at month one.

3 All of these quality of life instruments,  
4 I explained in detail in your briefing material, in  
5 appendix 4 pages 9 to 13. These exploratory analysis  
6 is no longer randomized, but might give some insight  
7 into the association of quality of life outcomes with  
8 being a normal sinus rhythm.

9 Each column contains a mixture of patients  
10 on Dofetilide and placebo. Of the 269 patients in  
11 normal sinus rhythm, 217 were on Dofetilide, and 52  
12 were on placebo, whereas 136 patients in atrial  
13 fibrillation included 85 patients on Dofetilide, and  
14 51 patients on placebo.

15 Looking at the SF36 physical function, 67  
16 percent of patients in normal sinus rhythm show an  
17 improvement, compared to 49 in atrial fibrillation.

18 The improvement seen in 6 out of the 8  
19 instruments suggests an association between normal  
20 sinus rhythm, and improved quality of life.

21 Having established the plausibility of an  
22 association between normal sinus rhythm and quality of

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1 life we examined quality of life by treatment group.

2 The analysis shown here is a percentage of  
3 patients with improvement at one month from baseline  
4 values across the eight quality of life instruments.

5 Patients randomized to 500 microgram BID  
6 in blue are compared with patients receiving placebo  
7 in red.

8 You can see that six of the eight  
9 instruments show various degrees of improvement for  
10 patients on Dofetilide compared to those on placebo.  
11 Similar trends were observed at six and twelve months,  
12 with data from month one as showing you the greatest  
13 effects.

14 This difference was more pronounced for  
15 instruments which may be considered more relevant in  
16 patients with atrial fibrillation. The SF36 physical  
17 function, the psychological well being score and  
18 design symptom score, with nominal P values less than  
19 .05.

20 In study 120 we use a questionnaire to  
21 assess arrhythmia related symptoms of fatigue, worry,  
22 chest pain, lightheadedness, shortness of breath, and

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1 palpitations.

2 Both frequency and severity were recorded  
3 using the point scale system. All symptoms were  
4 collected at two week's intervals to the end of the  
5 trial. For patients who had missing data or who  
6 dropped out of the study, the last observation was  
7 carried forward in this analysis.

8 This slide shows reduced frequency for  
9 system for patients in normal sinus rhythm as compared  
10 to atrial fibrillation. In this graph bars moving  
11 downward represent reduction in symptom frequency  
12 compared to baseline, whereas bars moving upwards  
13 represent an increase in symptom frequency.

14 For example, patients in sinus rhythm  
15 experience less frequent worry than those in atrial  
16 fibrillation. The trend toward frequency reduction  
17 was observed across all symptoms in patients who  
18 maintained normal sinus rhythm, with the most  
19 noticeable effects seen for worry, shortness of  
20 breath, and palpitations.

21 Similar trends were seen for symptom  
22 severity. Analysis of symptoms by treatment group,

1 shown here for the Dofetilide 500 microgram BID  
2 patients in blue, and for placebo patients in red,  
3 demonstrates an overall trend in symptom severity and  
4 frequency reduction in favor of the Dofetilide  
5 treatment group.

6 This favorable trend is apparent despite  
7 the delusional effect of mixed rhythm status within  
8 each treatment group, although no differences reached  
9 statistical significance.

10 In the frequency and severities cause the  
11 benefits of Dofetilide is most apparent for the  
12 symptoms of fatigue and shortness of breath. These  
13 data suggest that there is symptomatic benefit in  
14 patients treated with Dofetilide, possibly through the  
15 maintenance of normal sinus rhythm.

16 The FDA reviewers, Dr. Ganley and Dr. Hung  
17 analyzed 120 symptom data setting a different way, as  
18 is shown in table 120.21 of FDA's medical and  
19 statistical review of the efficacy data.

20 Using a categorical approach of symptom  
21 improvement, no change, or worsening, they confirmed  
22 the finding that patients in normal sinus rhythm

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1 experience an improvement in symptoms.

2 Now I will discuss conversion to normal  
3 sinus rhythm. Patients in studies 345 and 120 entered  
4 the trial with chronic atrial fibrillation or atrial  
5 flutter. All patients were initially given the  
6 opportunity to pharmacologically convert to normal  
7 sinus rhythm on randomized study treatment.

8 Both of these studies, 345 and 120,  
9 provide clear evidence for efficacy in conversion of  
10 atrial fibrillation and flutter to normal sinus rhythm  
11 with strong statistical significance.

12 This slide shows pharmacological  
13 conversion of atrial fibrillation to normal sinus  
14 rhythm in studies 345. The Y axis represents a  
15 probability of converting to normal sinus rhythm, and  
16 the X axis is a time to pharmacological conversion in  
17 hours.

18 There is a significant difference between  
19 the proportion of patients in sinus rhythm at day 3,  
20 which is a pre-specified endpoint for conversion.

21 For patients on Dofetilide 500 microgram  
22 BID 29 percent converted compared to 1 percent on

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1 placebo, statistically significant was the P value of  
2 .001.

3 Seventy percent of the patients that  
4 converted did so within the first 24 hours. Patients  
5 that did not convert pharmacologically were  
6 subsequently DC cardioverted.

7 Here is the conversion data for study 120.  
8 There is a significant difference between the  
9 proportion of patients converting to normal sinus  
10 rhythm between Dofetilide 500 microgram BID, 30  
11 percent; and placebo 1 percent. Statistically  
12 significant was the P value of less than .001.

13 As in studies 345, approximately 70  
14 percent of the converted patients did so within the  
15 first 24 hours.

16 This slide demonstrates a positive dose  
17 response relationship across the two trials, with 500  
18 microgram BID being the most effective dose.

19 To summarize, two large double blind  
20 placebo control trials showed efficacy and conversion  
21 of normal sinus rhythm with high statistical  
22 significance.



1 Similar to the dose response relationship  
2 seen in the maintenance of normal sinus rhythm there  
3 was also a dose response relationship in conversion of  
4 atrial fibrillation.

5 The data that I've presented show that  
6 Dofetilide is efficacious for maintenance of chronic  
7 atrial fibrillation or flutter, as shown in two  
8 placebo control trials, with more than 1,100 patients.

9 More than 70 percent of patients  
10 randomized to 500 microgram BID have been dosed  
11 according to the proposed treatment algorithm.

12 Efficacy is also demonstrated in subgroups  
13 and in patients whose dose was adjusted by the  
14 treatment algorithm. Maintaining patients in normal  
15 sinus rhythm was correlated with decreased arrhythmia  
16 related symptoms, severity, and frequency, and  
17 increased quality of life.

18 Furthermore, two placebo control trials  
19 demonstrate that Dofetilide is superior to placebo for  
20 conversion of atrial fibrillation and atrial flutter.

21 Thank you very much.

22 I would like to introduce the next

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1 speaker, Dr. Craig Pratt, who will talk about the  
2 safety presentation.

3 DR. PRATT: Dr. Califf, Dr. Lipicky, Dr.  
4 Temple, and members of the Committee, and ladies and  
5 gentlemen, good morning, almost good afternoon now.

6 The next topic is safety, and I would like  
7 to begin with the next slide, please.

8 What I propose to do is to go through in  
9 sort of a logical fashion, issues relating primarily  
10 to survival, because I think where we are all going  
11 with this, is there a mortality signal that translates  
12 from the Torsade that is inevitable in a drug that  
13 causes QT prolongation, as Dr. Lipicky has pointed out  
14 in his three day dissertation.

15 And I'm going to focus on proarrythmia  
16 with mostly talking about Torsade, other potential  
17 proarrythmias and other adverse events.

18 Now, as we pointed out, this was a large  
19 program, of over 6,000 patients, of which over three  
20 thousand were in clinical trials of SVA. I'm going to  
21 focus, repeatedly, on four populations comprising a  
22 wide spectrum of risk.

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1 I will repeat this sequence throughout  
2 each safety category. The first will always consist  
3 of the SVA trials relevant to the pivotal trials  
4 you've just heard about. The second will be the very  
5 important 3,228 patients in the Diamond trials  
6 comprising patients at high risk, and it will include  
7 a look at the group of patients, over 500 of them, in  
8 these trials, with LV dysfunction, and atrial  
9 fibrillation at baseline.

10 This survival analysis, I think, is quite  
11 relevant in establishing the safety of Dofetilide in  
12 treating atrial fibrillation, and we will move on.

13 As you have heard, from previous speakers,  
14 in the whole issue of safety revolves around the  
15 appropriate use of the algorithm which was derived  
16 through the experience in this entire program.

17 The renal function algorithm was added,  
18 and you can see that time course on figure 2 page 17  
19 of your document, and it reflects QT prolongation  
20 adjustment, as well as the renal function adjustment.

21 And as a result of this individualized  
22 approach, emphasizing safety, it is clear that many

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1 patients randomized to receive Dofetilide 500  
2 micrograms BID actually received lower doses.

3 So let me first now, focusing on survival,  
4 turn to the dosing algorithm in the ten placebo  
5 control trials.

6 Listed here are the reasons for dosage  
7 adjustment or discontinuation in these trials. Page  
8 88 in your document has a lot of details about this  
9 information.

10 You can see that ten patients had  
11 discontinuation of Dofetilide due to Torsade. An  
12 additional 37 required discontinuation due to QT  
13 prolongation.

14 Then we have dosage adjustment, and I  
15 think this is really pivotal in understanding the  
16 survival data because a large number of patients had  
17 their dosage decreased for creatinine clearance, or QT  
18 prolongation.

19 And this is a fact, I believe, really  
20 contributes to long term safety, and you will see the  
21 same data in the Diamond set.

22 So turning first to survival in the SVA

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1 analysis. This compares placebo to Dofetilide with  
2 reference to total mortality in the relatively low  
3 risk patients in these placebo controlled SVA trials.

4 Analysis is by intention to treat, and  
5 this is evaluated by the Kaplan-Meier estimate with  
6 one year follow-up.

7 If you look at the baseline  
8 characteristics here there are no significant  
9 differences in Dofetilide and placebo assigned  
10 patients relative to risk for mortality, including the  
11 gender, age, structural heart disease, and other  
12 issues that you see listed on this slide.

13 You've seen the Kaplan-Meier analysis in  
14 your document, it reveals no significant mortality  
15 difference between the groups, but we acknowledge the  
16 fact that there is a small number of events, and  
17 whatever we say about this group, wide confidence  
18 intervals surround the attempt to make a point  
19 estimate of mortality.

20 So let's show you four such attempts on  
21 the next page. So here we have four analysis. The  
22 pooled survival analysis, these first two analysis

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1 were actually conducted at Duke by Dr. Pritchard and  
2 associates, and these represent all patients in the  
3 pivotal placebo controlled SVA trials, and it revealed  
4 the relative risk of 1.4 unadjusted, and 1.1 adjusted  
5 when the analysis was adjusted for baseline  
6 imbalances.

7 Now, I just want to mention what those  
8 imbalances are. It is important to realize that the  
9 proportion of Dofetilide patients who had chronic or  
10 persistent, as Peter said today, atrial fibrillation  
11 were randomized three to one, in 120 and 345, and  
12 therefore there is an excessive number of those  
13 patients, and there are also differences that were  
14 adjusted for age, gender, and structural heart  
15 disease. So those were the adjustments made, and  
16 these two point estimates were obtained.

17 There are many other described looks at  
18 this data with point estimates that range in this  
19 area. And you have them in your document on pages 90  
20 through 93.

21 If one wants to look at subgroups with so  
22 few deaths, one can look at subgroups like gender,

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1 presence or absence of structural heart disease, and  
2 those are the point estimates that one obtains with  
3 those, with obviously extremely wide confidence  
4 intervals.

5 What I want to do now is turn to  
6 supporting safety mortality that the committee has not  
7 previously experienced in terms of evaluating an  
8 antiarrhythmic drug for atrial fibrillation. And the  
9 population strongly supporting this safety are the  
10 Diamond trials, whose background is presented in  
11 detail in section E of your document.

12 All patients had structural heart disease  
13 and LV ejection fraction equivalent to, or equal or  
14 less than 35, based on the wall motion index. Both  
15 these trials are randomized, placebo controlled,  
16 double blind studies, with most patients assigned to  
17 either placebo or Dofetilide 500 micrograms BID.

18 More than 80 percent of the patients were  
19 treated with the dosing algorithms similar to the SVA  
20 approach and the primary endpoint was all-cause  
21 mortality evaluated by the Kaplan-Meier analysis, and  
22 the analysis was by intention to treat.

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1 Obviously the original trial was designed  
2 to show superiority of Dofetilide over placebo.

3 The two trials differ in that the heart  
4 failure trial focuses on patients with clinical  
5 congestive heart failure, and this trial focuses on  
6 patients very early after myocardial infarction, both  
7 whom have LV systolic dysfunction.

8 The baseline demographic characteristics  
9 for both the Diamond CHF and Diamond MI trials known  
10 to be associated with mortality risk, are similar for  
11 Dofetilide and placebo assigned patients.

12 I won't go through the laundry list there,  
13 you've seen it. Patients in the Diamond CHF clearly  
14 had worse LV function, more severe functional  
15 impairment, than patients in the Diamond MI trial.

16 All-cause mortality, the primary endpoint  
17 of both of these trials are presented by the Kaplan-  
18 Meier plots. Placebo mortalities at one year in  
19 Diamond CHF is 28 percent. For Diamond MI 23 percent,  
20 emphasizing the high risk in these populations.

21 And as you can see, there is literally no  
22 mortality difference in either of these trials,

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1 between Dofetilide and placebo assigned patients. The  
2 hazard ration in Diamond CHF is 0.95, and 0.91 in  
3 Diamond MI.

4 Fairly narrow confidence limits are seen  
5 because of the fact that there are 1,101 deaths in  
6 these two trials. Overall there are 19 more placebo  
7 related death than there are Dofetilide associated  
8 deaths.

9 Since the issue of proarrythmia is  
10 important, a separate analysis of arrhythmic death is  
11 an important category. Now, these deaths are all  
12 classified by a committee, blinded by the drug  
13 assignment, and as with total mortality, there is no  
14 excessive arrhythmic death in either of the groups,  
15 with a total of six more patients classified as having  
16 an arrhythmic death on placebo, than on patients  
17 assigned to Dofetilide.

18 As in the SVA trials, safety was a  
19 principal motivation for requiring, number one, in-  
20 patient initiation, and ultimately, after about 400  
21 and some patients, the dosage adjustment algorithm  
22 that we've presented today.

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1           In the same format as in the SVA trials is  
2 a summary of the in-hospital dosage adjustments that  
3 were performed in the Diamond trials.

4           Now, a large percentage of Diamond  
5 patients had adjustment for creatinine clearance, and  
6 that stands to reason, given they had LV systolic  
7 dysfunction, and reduced renal function.

8           Some had adjustments for QTc, the  
9 discontinuations for Torsade, and excessive QT  
10 prolongation are listed.

11           While efficacy and safety are analyzed as  
12 intention to treat, they include almost 50 percent of  
13 patients, therefore, who had their dosage adjusted.  
14 The individualization of this dose is, really, I think  
15 a critical component in the long-term safe use of  
16 Dofetilide.

17           Now, since there is a total of 1,101  
18 deaths in the combined Diamond trials, exploratory  
19 analyses of clinically relevant patient subsets is, I  
20 think, potentially quite informative.

21           Presented here are hazard ratios and point  
22 estimates of such relevant subsets in Diamond CHF

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1 including gender, neo heart class, and the other ones  
2 that you see here, there were no subsets which showed  
3 a statistical difference in mortality between  
4 Dofetilide assigned and placebo assigned patients.

5 Quite similar results are seen in Diamond  
6 MI, with no significant differences between Dofetilide  
7 and placebo assigned patients.

8 Now, in the FDA questions the panel has  
9 been asked to consider the effect of ischemia. The  
10 Diamond MI population, in fact, is an early post-MI  
11 population of over 1,500 patients.

12 A subset of Diamond CHF and MI patients  
13 had clinical angina. If you look at that subset of  
14 patients with angina, which comprised over 800  
15 patients, the point estimates of mortality are 0.84  
16 and 0.98 for Diamond MI and CHF, respectively.

17 I want to turn now to this Diamond AF  
18 population, and I think the people that do care for  
19 atrial fibrillation patients frequently do appreciate  
20 the fact that this is a unique population.

21 These 506 patients are a little bit  
22 different than the rest of the Diamond patients, other

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1 than atrial fibrillation at baseline, they have a one  
2 year mortality of 32 percent, as compared to 24  
3 percent overall.

4 We think this represents a very robust  
5 sub-analysis, it is the largest long-term experience  
6 in patients with atrial fibrillation and significant  
7 structural heart disease in a randomized trial.

8 One important difference that we need to  
9 remember from the remainder of the Diamond patients,  
10 is that the initial Dofetilide dose for patients with  
11 atrial fibrillation was 250 micrograms BID, further  
12 modified, if necessary, by the treatment algorithm on  
13 an individual basis.

14 Now, this analysis is a predefined  
15 population, but this was a retrospective analysis.  
16 The total mortality was compared in those patients  
17 assigned to Dofetilide or placebo. All-cause  
18 mortality, again, by intention to treat, evaluated by  
19 Kaplan-Meier method, the one year estimate of  
20 mortality, as we mentioned, was nearly 32 percent.

21 Baseline characteristics in these two  
22 groups, as in the previous groups, are matched for

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1 risk with not statistically significant differences  
2 between treatment assignment.

3 The Kaplan-Meier analysis of the two  
4 atrial fibrillation treatment groups reveals identical  
5 mortality. There are five more placebo assigned than  
6 Dofetilide related deaths.

7 I want to call your attention to the fact  
8 that approximately 35 percent of the AF patients in  
9 Diamond were entered into a substudy, and that  
10 substudy has been presented and discussed in appendix  
11 6 of your document.

12 So this figure summarizes Dofetilide  
13 survival experience in these various trials, the SVA  
14 patients, the individual trials that were the pivotal  
15 trials for efficacy, with the advise that we did one  
16 year follow-up on every patient, regardless of whether  
17 or not the patient was still taking the study drug.

18 The Diamond CHF MI and AF populations, and  
19 these are the point estimates mortality, and their  
20 confidence limits for all those populations.

21 We believe that these overall results are  
22 reassuring, and they are closely related to the in-

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1 patient initiation in individualized dosage adjustment  
2 algorithm.

3 The next topic is proarrhythmia. Sudden  
4 cardiac death, although listed here, we've mentioned  
5 some issues related in sudden cardiac death in the  
6 Diamond trials.

7 I'm going to turn to the most important  
8 clinical issue concerning the committee, concerning an  
9 you of us as clinicians, and that is Torsade de  
10 points, ventricular tachycardia.

11 Now, the observed incidence of Torsade  
12 ventricular tachycardia in the same main patient  
13 peoples that I previously discussed, including the SVA  
14 trials, Diamond CHF, Diamond MI, and Diamond AF, are  
15 presented here.

16 It is important to realize that these  
17 include both pre and post-algorithm results.

18 There were no cases of Torsade in clinical  
19 pharmacology studies of 909 healthy subjects. Doses  
20 up to 1,250 micrograms BID. They are not included in  
21 the slide.

22 Now let's turn to the fact that 442

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1 Dofetilide assigned patients were entered prior to the  
2 initiation of the renal algorithm, and therefore one  
3 has the opportunity to observe the importance of  
4 adding renal function algorithm in these trials.

5 For instance, before adjustment of dose  
6 using creatinine clearance, the rate of Torsade in the  
7 Diamond trials was 3.1 and 4.7 percent, respectively.  
8 And this was reduced, after that algorithm was  
9 initiated, to 2.9 and 0.6 percent, respectively.

10 In the placebo controlled SVA trials you  
11 can see that 11 Dofetilide assigned patients developed  
12 Torsade des points ventricular tachycardia. Of these,  
13 ten were identified in the in-patient initiation  
14 phase, days one through three, and none of these  
15 patients died.

16 In the Diamond trials there were 32  
17 patients that had Dofetilide associated Torsade. Of  
18 these 23 were identified in the first three days. This  
19 doesn't necessarily result in in-patient or out-  
20 patient, because some of these patients had a longer  
21 hospitalization, but 23 of the 32 were first three  
22 days, of which 3 of those patients did die.

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1           Let's look at a little more detail about  
2 what happened to these patients. In the SVA trials 9  
3 of the 11 had symptoms, 8 required intervention, and  
4 no patients died.

5           For the Diamond trials 29 of the 32 were  
6 symptomatic, 23 required intervention, and 3 patients  
7 died.

8           In the Diamond AF trial you can see the  
9 same information as contained in the other parts of  
10 that slide.

11           A total of 8 cases of Torsade in the SVA  
12 program occurred in females, and 15 cases of Torsade  
13 in Diamond were female. 2 of the 3 deaths due to  
14 Torsade were female, the other was male. All patients  
15 developing Torsade had study drug immediately  
16 discontinued.

17           There were univariient and multivaried  
18 analysis done to look at the associations, and I think  
19 Dr. Kowey and others would tell you that, in fact,  
20 these looked to be similar to other drugs that are  
21 calcium blockers, that is there is an association,  
22 definitely, with female gender in the elderly,

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1 prolonged QTcs, obviously a reflection of dose, and  
2 the use of diuretics.

3 Now, in multivaried analysis gender, QTc,  
4 dose remain predictors of Torsade.

5 Let me briefly go to issues relating to  
6 other proarrythmia. In addition to Torsade there were  
7 other -- four other documented proarrythmia events,  
8 new sustained VT of VF in the SVA data base. However,  
9 we need to call your attention to the fact that these  
10 are, three of the four are double counted. That is,  
11 patients had Torsade, and they were also circled to  
12 have ventricular fibrillation, so all four of these  
13 represent only one new patient. The other three  
14 episodes occurred in patients that had Torsade. The  
15 only new one was a patient who was on Dofetilide 750  
16 micrograms BID, not a recommended dose.

17 In summary, Torsade is the primary  
18 clinically relevant proarrythmia, and the whole  
19 discussion this morning has reflected the fact that it  
20 is the committee's principal concern.

21 The occurrence of Torsade can be  
22 minimized, not eliminated, but minimized by the dosing

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1 algorithm. We feel the clinical consequences of  
2 Torsade are minimized by in-patient initiation of  
3 Dofetilide, and the insistence of three days of  
4 monitoring.

5 The results of this cautious dosing  
6 algorithm for Dofetilide is no increase in mortality  
7 over a wide range of risk groups.

8 Let me turn briefly to other adverse  
9 events, the focus being on the SVA placebo controlled  
10 trials. You've seen many versions of this in your  
11 document around page 124. I only present one of them,  
12 we could present many others.

13 Listed here are the 10 SVA placebo  
14 controlled trials, the most prevalent adverse events,  
15 occurring at any time, adjusted for years of exposure.

16 Although there are small numerical  
17 differences observed, none are significant. There are  
18 also no differences in a similar table on page 124 of  
19 adverse events requiring discontinuation.

20 I think it is relevant to look at issues  
21 that are morbidity issues, like total hospitalizations  
22 for heart failure. It is certainly a relevant long-

1 term measure of safety, and we are looking at this in  
2 the Diamond trials presented here.

3 Dofetilide assigned patients, as you can  
4 see, had fewer hospitalizations than placebo assigned  
5 patients. Similar results would be observed if we  
6 showed you the same curves for total hospitalizations.

7 I'm making no claim at this time, I'm just  
8 saying, at the very least, there is no evidence for  
9 increased Dofetilide associated morbidity as assessed  
10 by two measures of hospitalization, either for CHF or  
11 all-cause hospitalization.

12 I would also like to say, though, that I  
13 think you will find some intriguing results in the  
14 Diamond AF population that will be discussed by Dr.  
15 Ruskin in his risk benefit assessment.

16 Now, myself, Dr. Ruskin, everyone involved  
17 with the Dofetilide program realized that the  
18 appropriate clinical concern with an antiarrhythmic  
19 drug is the risk of Torsade, and it may be associated  
20 with mortality.

21 So we really have to look at the  
22 relationship to address this. Please allow me to

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1 narrate this busy slide.

2 The data come from the Diamond population  
3 combined with the 10 SVA populations. On the left-  
4 hand side is a summary of the univariate analysis that  
5 we've already presented for some of the relevant  
6 issues that relate to risk of Torsade.

7 On the right-hand side is an analysis of  
8 the identical subgroups to examine whether we see an  
9 increase in mortality in Dofetilide compared to  
10 placebo.

11 For instance, taking gender, which is  
12 extraordinarily important, the relative risk of having  
13 Torsade is definitely increased if you are female, but  
14 the mortality analysis in females, in all the  
15 populations we've looked at shows a relative risk  
16 estimate that is less -- at least at one.

17 Similar results demonstrating the absence  
18 of increased mortality in Dofetilide compared to  
19 placebo are seen for the elderly population, QTc at  
20 baseline, and the presence of structural heart  
21 disease.

22 Now, I'm going to just go back, this is on

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1 figure 2 page 17 of your document. This is just a  
2 list of all these trials. I know that most people  
3 can't really read those, except those sitting up very  
4 close, and this is when the creatinine clearance  
5 algorithm was initiated.

6 And so I think it is pretty relevant that  
7 realizing there was a learning curve in this  
8 development program over 8 years, that one could look  
9 at, an additional safety analysis focusing only on  
10 those patients who are put in the trials, after the  
11 initiation of this algorithm.

12 These populations being evaluated are  
13 identical to those previously represented, that is the  
14 SVA and Diamond trials.

15 Now, the more than 3,200 patients are  
16 included in this analysis, including SVA patients,  
17 randomized after creatinine clearance algorithm to the  
18 500 dose, the dose which we intend to use.

19 The Diamond CHF and MI populations for all  
20 then non-AF patients randomized to the creatinine  
21 clearance, after the creatinine clearance amendment,  
22 and then very importantly, we take the group in the

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1 Diamond AF population, randomized after the creatinine  
2 clearance amendment, that would have received 250 BID  
3 or less because of this creatinine clearance.

4 So I think it is all the populations  
5 clinically relevant to the way we intend to use the  
6 drug.

7 The results of this analysis are  
8 essentially they emulate the proposed clinical use of  
9 the drug. The SVA trials are 550 Dofetilide assigned  
10 patients, the Torsade rate is 0.8 percent, and the  
11 hazard ratio is less than one.

12 For the Diamond trials a total of 1,722  
13 patients there is the Torsade rate overall, there is  
14 the point estimate of mortality, and you can go to  
15 Diamond trials alone, or you can go to the Diamond AF  
16 population, and those are the point estimates of  
17 mortality, as compared to the risk of Torsade de  
18 points ventricular tachycardia, and used correctly  
19 there is no mortality signal.

20 Now, Dr. Califf, I was going to make this  
21 a concluding slide, but you've asked me to go ahead  
22 with a couple other slides, so let me just say that I

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1 was going to conclude, but based on what you've seen,  
2 there is no adverse effect on mortality, even in  
3 patients with severely compromised cardiovascular  
4 disease or function.

5 In patient initiation the dose  
6 individualization is very important in identifying and  
7 either lowering the dose, or eliminating these  
8 patients from further therapy.

9 And we think that the adherence to the  
10 dosing algorithm minimizes the consequences of the  
11 proarrythmia that is clearly there.

12 And in terms of other adverse events,  
13 there is no other differences that are clinically  
14 relevant from placebo.

15 Now, where I would like to take you from  
16 there, because of the previous conversation, and a  
17 discussion I had with Dr. Califf at the break, is the  
18 drug interaction document.

19 And you did have that as a supplement to  
20 your many documents that you had, and we apologize  
21 they didn't all come at identical times.

22 But that drug interaction document is

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1 important, and let me just remind you, before we get  
2 any slides on, why don't we just take that slide off  
3 right now.

4 This is an analysis, then, of all the SVA  
5 and all the Diamond patients, 5,051 patients, in whom  
6 there was a great deal of long term follow-up, because  
7 it includes over 3,000 Diamond patients.

8 If you want to start reading about the  
9 concomitant meds these patients were on, you can start  
10 on page 11 of that document. But you will see that  
11 over 2,300 of these patients were on Digoxin, over 900  
12 patients were on calcium blockers.

13 And there was a lot of long-term follow-up  
14 since, in fact, Diamond contributed 3, 028 of these  
15 patients. And we are looking at a data base in which  
16 there was 43 cases of Torsade de points ventricular  
17 tachycardia.

18 You know, before I show you the data, I  
19 think it is fair to say there is some real world data  
20 here, and I would like to tell you why. First of all,  
21 in Diamond the average age of the patients was 70  
22 years old.



1           These patients were treated in local  
2 hospitals in Denmark. In fact, over half the  
3 population in Denmark was involved in the 37 general  
4 hospitals.

5           Many of the doctors there were internists  
6 and general practitioners, they were not all  
7 cardiologists, and certainly not all  
8 electrophysiologists.

9           In fact, the QT was often measured by  
10 junior physicians, and even nurses. So I think this  
11 does, in that respect, reflect some of the real world  
12 issues that we would like to know about.

13           The drugs weren't supplied some way  
14 special. They were put in bottles, and there was very  
15 extensive concomitant medication use not only at  
16 baseline, but during the trial. In fact, almost half  
17 of the patients had between one and five new  
18 concomitant medications.

19           So, with that, let me go to backup slide  
20 18, and we will follow that by 22 and 21, just for  
21 your information.

22           So this is the population, and I don't

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1 think it is insignificant. It is a lot of  
2 information, and it is the best information we have to  
3 try to address the questions which were very  
4 appropriately being the item of concern earlier today.

5 And we are going to examine the  
6 relationship between the occurrence of Torsade and  
7 mortality. And I think you've already seen that some  
8 of these drugs do have a relationship, albeit somewhat  
9 confounded by indication.

10 Here is sort of the top list of drugs. We  
11 have a number of patients. This is actually  
12 incorrect, we have almost 400 patients on Diltiazem,  
13 almost 425 patients on Diltiazem, another couple  
14 hundred on Verapamil, a total of about 900 in calcium  
15 blockers. You can see the number of people that are  
16 taking Digoxin, it is a very large group of patients.

17 So that is the concomitant medication.  
18 That is just baseline medications. Just to let you  
19 know, 93 percent had at least one concomitant medicine  
20 added or subtracted during the trial, 48 percent six  
21 to ten -- 25 percent, six to ten new concomitant  
22 medicines. So there is a lot of medicine changes

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1 going on, all the things that we would be concerned  
2 about.

3 And this is the bottom line for the data  
4 that we have. Here is mortality, and here is the  
5 relative risk in these population, including Digoxin,  
6 including Verapamil, including all the other fairly  
7 complicated metabolic groups that Dr. Brater so  
8 elegantly discussed earlier. And that is the result  
9 of that analysis.

10 And with that, Mr. Chairman, I will stop.

11 ACTING CHAIRMAN CALIFF: We have seen a  
12 lot of data, we don't need to see the same data over  
13 and over, but if you have new perspectives to add, we  
14 would certainly like to hear it.

15 DR. RUSKIN: Dr. Califf, Drs. Lipicky and  
16 Temple, members of the Committee, ladies and  
17 gentlemen, I will do my best to stick to that 15  
18 minute limit, and share with you some thoughts about  
19 the benefit risk evaluation of this agent.

20 What I would like to do is offer some  
21 comments about the therapeutic benefits of Dofetilide  
22 in treating atrial fibrillation, and share with you a

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1 little bit of additional data, offer some comments on  
2 the risks of Dofetilide, in low and high risk  
3 patients.

4 And to the extent that the data permit,  
5 attempt to place in perspective the benefits and risks  
6 of this drug, that is its efficacy and its safety, in  
7 relation to currently available therapeutic agents.

8 As you've heard, Dofetilide results in  
9 conversion of atrial fibrillation to sinus rhythm in  
10 approximately 30 percent of patients with chronic  
11 atrial fibrillation, and among those patients  
12 converted to sinus rhythm, either pharmacologically,  
13 or electrically, about 60 percent remained in sinus  
14 rhythm, on the drug, at one year of follow-up.

15 This maintenance of sinus rhythm is  
16 associated with symptomatic benefit.

17 This slide summarizes for you average  
18 efficacy rates for a variety of agents reported in the  
19 literature, specifically with reference to maintenance  
20 of sinus rhythm after conversion of persistent atrial  
21 fibrillation.

22 And as you can see, for Dofetilide, as

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1 you've heard, Quinidine, Disopyramide, Flecainide and  
2 Sotalol, the efficacy rates at one year are roughly  
3 comparable, that is, in the range of 50 percent.

4 And I think most people would agree that  
5 their clinical experience fits with that number. It  
6 is likely that Amiodarone is somewhat more effective,  
7 with an efficacy rate in the range of 70 percent at  
8 one year, compared with these other available agents.

9 Now, you've heard from Dr. Pratt about the  
10 subset of patients in the Diamond AF trial, these are  
11 506 patients drawn from Diamond MI and Diamond CHF who  
12 had atrial fibrillation at the time of entry into the  
13 study.

14 You've also heard that the survival  
15 analysis in this population showed no difference  
16 between Dofetilide and placebo for all-cause  
17 mortality.

18 Among these 506 patients, 234 converted to  
19 normal sinus rhythm at some point during the trial.  
20 And this slide summarizes for you the time to  
21 recurrence of atrial fibrillation among the 234  
22 converters.

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1           And as you can see there were 148  
2           convertors on Dofetilide, versus 86 on placebo, and  
3           that time to recurrence was much later on Dofetilide  
4           than it was on placebo following recurrence, yielding  
5           an 80 percent preservation of sinus in convertors on  
6           Dofetilide versus 42 percent on placebo at 12 months.

7           You've also heard about an analysis that  
8           was performed in the Diamond trials. This was a pre-  
9           specified endpoint examining time to hospitalization  
10          for congestive heart failure, for worsening congestive  
11          heart failure.

12          And what you see on this slide are two  
13          sets of Kaplan-Meier curves displaying time to  
14          hospitalization for CHF in Dofetilide versus placebo  
15          treated patients. In the CHF trial, versus the MI  
16          trial, there was a significant difference here in  
17          hospitalization rates for heart failure on Dofetilide  
18          versus placebo, yielding a hazard ratio of .75. This  
19          effect was not seen in the Diamond MI study.

20          The obvious question that arises here is  
21          whether or not this effect on heart failure has  
22          anything to do with rhythm status, whether it may in

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1 fact be mediated by an effect on cardiac rhythm, since  
2 there is no other obvious way that the drug should  
3 improve hospitalization rates for heart failure.

4 And so similar analysis was performed  
5 among the patients in Diamond AF. The 506 with AF at  
6 entry into the Diamond trial. And as you can see this  
7 benefit that was observed overall in the Diamond CHF  
8 trial is in fact more prominently evident in the  
9 Diamond AF subset, that is time to first  
10 hospitalization for worsening congestive heart failure  
11 is significantly reduced in the Dofetilide compared  
12 with placebo treated patients, yielding a hazard ratio  
13 of .69.

14 TO further asses the relationship between  
15 rhythm status and impact on heart failure  
16 hospitalization, the same analysis was performed for  
17 time to hospitalization for heart failure in all the  
18 Diamond patients, excluding those who had atrial  
19 fibrillation at the time of entry into the trial.

20 And you can see that this impact on heart  
21 failure hospitalization is largely lost.

22 So what we see here, then, is similar to

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1 what you observed in the SVA trials. That is,  
2 Dofetilide is associated in this very sick population  
3 with a higher conversion rate from atrial fibrillation  
4 to sinus rhythm, a higher maintenance rate of sinus  
5 rhythm, compared to placebo, and an associated  
6 reduction in hospitalization rates for congestive  
7 heart failure.

8 Because of the concern that this effect  
9 might be mediated by hospitalization for other causes,  
10 or drop outs for other reasons, or mortality, the same  
11 analysis was performed, that is time to all-cause  
12 hospitalization in the Diamond AF population, as well  
13 as a composite analysis of time to all-cause  
14 hospitalization death and withdrawal.

15 And you can see that the salutary effect  
16 of Dofetilide compared to placebo is maintained in  
17 this analysis, and in this composite analysis,  
18 although the effect is attenuated by including  
19 mortality.

20 You've heard that Dofetilide is, in fact,  
21 a well tolerated drug, and that it is not discontinued  
22 at a rate in excess of that of placebo for non-cardiac

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1 side effects.

2 The primary risk of Dofetilide is  
3 proarrythmia, Torsade de points, and you've heard a  
4 detailed discussion of that by Dr. Pratt. I would  
5 like to just offer a few comments with regard to rates  
6 for this drug in relation to other agents.

7 The overall rate of Torsade in the SVA  
8 placebo controlled trials was 0.8 percent, which is  
9 quite comparable to what has been seen with other  
10 antiarrhythmic agents which affect repolarization, and  
11 you've also heard that the risk of Torsade can be  
12 minimized by the dosage adjustment algorithm, and its  
13 consequence is limited by in hospital initiation, both  
14 critical cornerstones to the safe use of this agent.

15 These are data from the literature on  
16 Torsade rates with other agents. The Dofetilide data  
17 are shown here for the SVA population, these are in  
18 placebo controlled studies, and this is for all  
19 patients receiving Dofetilide, the remainder of these  
20 are drawn from the literature, Sotalol, with a 1.4  
21 percent rate in an SVA population, and Quinidine,  
22 Procainamide, and Disopyramide shown here.

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1           And I think one can conclude, that to the  
2           best that one can compare these, and there are  
3           certainly some differences in populations, there is no  
4           obvious glaring excess of Torsade in this drug in  
5           relation to other agents known to cause the problem.

6           Amiodarone causes Torsade de points very  
7           rarely, as emphasized by Dr. Graboys, and I should  
8           emphasize that this represents only a single case in  
9           an AF population.

10           In the CHF Stat trial, which I will  
11           mention in a minute, which was a large heart failure  
12           trial with Amiodarone there were no cases of Torsade  
13           reported.

14           I will spend only ten seconds on this to  
15           reemphasize the point that Dr. Pratt made, and that is  
16           the univariant predictors of risk for Torsade are  
17           known for this drug, and they apply to virtually all  
18           drugs that cause Torsade, and they include gender,  
19           age, baseline QT, and the presence of structural heart  
20           disease.

21           But in this large very rich data base,  
22           these factors, which are known to predict Torsade, did

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1 not predict mortality in patients receiving  
2 Dofetilide.

3 The next several slides will address the  
4 issue of mortality and again to attempt, to the extent  
5 that the data permit, to place it in perspective in  
6 relation to other available antiarrhythmic agents.

7 These are data from the SVA trials, and I  
8 won't belabor this point, because you have seen these  
9 presented in Dr. Pratt's talk. The point that I do  
10 want to make is that what we are talking about here  
11 are very small numbers of events, so that it is  
12 difficult to place any confidence in the hazard ratios  
13 that are -- in the point estimates of the hazard  
14 ratios that are obtained, and the lack of confidence  
15 is expressed in this very wide confidence intervals.

16 This is a problem with all data bases of  
17 this type, that is a relatively low risk population  
18 with a very low mortality rate. This is an issue that  
19 has been faced with every antiarrhythmic drug that the  
20 Agency has seen.

21 One of the analysis that was done, and  
22 again, it doesn't definitively answer the question, by

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1 any means, but I show it to you because I thought the  
2 data was important to present, was an analysis of  
3 survival in all patients in the two pivotal AF trials,  
4 120 and 345.

5 That is a 12 month mortality assessment in  
6 every patient in both trials. And there was 100  
7 percent follow up.

8 This analysis obviously is limited in the  
9 sense that most patients on placebo either end up on  
10 something else or nothing, because they recur, and  
11 many patients on Dofetilide, throughout the course of  
12 this study, end up either on nothing, or some other  
13 drug.

14 But it is a real world look and one of the  
15 only real world looks we can get at one year, in an  
16 SVA population. And when that was done for these two  
17 studies, and as I mentioned with 100 percent follow  
18 up, there was no strong signal here of an excess  
19 mortality risk.

20 Now, I must emphasize that it is not  
21 possible, based on this data, to exclude some excess  
22 mortality risk associated with the use of Dofetilide

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1 in this low risk population. One simply cannot  
2 exclude that possibility from these data.

3 In the past this is pretty much the limit  
4 of what the Agency has seen in reference to  
5 antiarrhythmic drug applications. And the concern has  
6 always been how do we know we are not missing a much  
7 bigger signal, and yes we have a drug that looks as if  
8 it has efficacy, but you are looking at a low risk  
9 population, and we know that this agent is going to be  
10 used in much sicker patients.

11 How can we possibly assess the risk benefit  
12 ratio in that group, and how do we know that there  
13 will not be an enormous increase in mortality when the  
14 drug is given to higher risk patients.

15 And I would like to just offer some  
16 comments specifically addressing that question in the  
17 next several slides.

18 Let me -- this is simply a reiteration of  
19 what you've seen for Dofetilide in the SVA data base  
20 showing an all-cause mortality rate of 1.3 percent,  
21 versus .9 in the placebo control population, compared  
22 with the Quinidine beta analysis with a 2.9 percent

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1 one year mortality rate, with what appears to be a  
2 roughly comparable control group.

3 The arrhythmic date rate on Dofetilide was  
4 not different from that seen with placebo, and in the  
5 Quinidine meta analysis it was 1 percent versus .3 in  
6 the controls.

7 And I think all one can say from these  
8 data, again, in a group with a low event rate, is that  
9 there is no obvious signal here that Dofetilide is  
10 associated with a markedly increased risk compared  
11 with a drug like Quinidine, which remains the most  
12 commonly prescribed drug for atrial fibrillation.

13 Now, let me get beyond this because my  
14 comments on the previous slide related to the question  
15 of what happens with sicker populations.

16 And I think for the first time, and with  
17 the exception of Amiodarone, the only time that we  
18 have these kinds of safety data are in this data base.

19 This is a composite slide showing you  
20 hazard ratios for all-cause mortality as a function of  
21 antiarrhythmic drug class in post-infarction patients.  
22 And I show this because we have data in these

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1 populations. That is extensive data, with many  
2 different classes of antiarrhythmic drugs.

3 And you are all familiar with the fact  
4 that the data on class IA drugs is quite limited, but  
5 it is not encouraging in terms of safety. Certainly  
6 a trend in most of the studies to an adverse effect on  
7 mortality.

8 As discussed in the public comment period  
9 the cardiac arrhythmia suppression trial established a  
10 very substantial excess mortality rate when the class  
11 IC drugs are used in a patient population with  
12 coronary artery disease, and recent myocardial  
13 infarction.

14 The beta blockers are the only class of  
15 drugs that have very clear and definitive evidence of  
16 a mortality benefit in this population.

17 The calcium blockers are neutral effect.  
18 Amiodarone in the European trial, a neutral effect.  
19 A slightly favorable trend in CAMIAT, and if one were  
20 to pool these two, one would end up with a hazard  
21 ratio of just over .9, almost identical to what is  
22 seen in the Diamond MI trial, a 1,500 patient post-MI

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1 mortality trial in patients with recent infarcts and  
2 impaired ventricular function.

3 I should also contrast this data with the  
4 D-Sotalol trial, the Sword study, this is a pure class  
5 3 agent that was also studied post-infarction in which  
6 there was a clear demonstration of harm with regard to  
7 excess mortality.

8 One of the concerns that comes up,  
9 whenever you see a neutral effect on mortality in a  
10 sick population is whether or not the drug may, in  
11 fact, be having two effects; an antiarrhythmic effect  
12 in some subsets, and a proarrhythmic effect in other  
13 subsets, resulting in a neutral impact on mortality.

14 And while there is no way to deal with  
15 that question definitively, I thought it would be  
16 interesting to just take a quick look at the Sword  
17 data, in which there was at least an adverse effect in  
18 a very select subset of patients, and to compare that  
19 with the data that we do have available for the  
20 Diamond MI trial.

21 These are Kaplan-Meier curves from the D-  
22 Sotalol mortality trial in which the drug was compared

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1 to placebo in post-infarction patients who were  
2 stratified either by recent myocardial infarction  
3 versus remote, or by severe LV dysfunction versus  
4 moderate LV dysfunction.

5 And the only point that I want to make is  
6 that there was no subgroup here that showed benefit,  
7 but there was a striking adverse effect in patients  
8 with moderate left ventricular dysfunction, and remote  
9 infarction, in whom there appeared to be unmasking of  
10 a proarrhythmic effect in a subset that had a very low  
11 placebo event rate, accounting presumably for much of  
12 the adverse mortality effect, although there was  
13 certainly no favorable effect in these other groups.

14 In analyzing the results of the Diamond MI  
15 trial, stratified by moderately severe and severe LV  
16 dysfunction, there was no evident difference in terms  
17 of a subset in which Dofetilide appeared to be having  
18 an adverse effect on outcome.

19 Now, what about congestive heart failure?  
20 Fortunately we have some comparative data, and I  
21 apologize for the imperfection of this part of the  
22 curve, this was scanned.

1           What it shows you are Kaplan-Meier curves  
2           for all-cause mortality in the CHF stat and the  
3           Diamond CHF trials, two very similar trials; the CHF  
4           stat study being carried out with Amiodarone in  
5           patients with severe LV dysfunction and congestive  
6           heart failure, and frequent ventricular premature  
7           beats versus the Diamond CHF study which you've heard  
8           about.

9           And I emphasize this, the importance of  
10          this study, because at the present time Amiodarone is  
11          really the most widely used agent for the treatment of  
12          symptomatic atrial fibrillation in patients with  
13          congestive heart failure.

14          What was seen in the CHF stat trial was  
15          virtually an identical, that is neutral mortality  
16          effect to what was seen in the Diamond CHF trial, and  
17          the mortality rates were very similar in the two  
18          studies.

19          In addition, analysis have been performed  
20          in both trials for patients who entered the trial with  
21          atrial fibrillation. And you've heard about the  
22          Diamond AF trial. In the CHF stat trial there were

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1 103 patients who entered the trial in atrial  
2 fibrillation, roughly 15 percent of patients in both  
3 studies.

4 In looking at the efficacy of agents in  
5 converting atrial fibrillation to sinus rhythm, there  
6 were significant differences in placebo efficacy rates  
7 between the two trials. And I don't know whether this  
8 reflects differences in populations, or in the ways in  
9 which presence or absence of AF was determined.

10 But if one examines the placebo subtracted  
11 efficacy rate for conversion of AF to sinus rhythm,  
12 the effects of Amiodarone and Dofetilide in this very  
13 sick population are virtually identical.

14 This is the next to the last slide, and it  
15 represents a modification of a figure published in the  
16 recent review of therapeutics for atrial fibrillation,  
17 and emphasizes the fact that in patients without  
18 structural heart disease and symptomatic AF we have a  
19 number of therapeutic options available from virtually  
20 all classes of antiarrhythmic drugs.

21 In patients, however, with ischemic heart  
22 disease and in particular those with congestive heart

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1 failure, the therapeutic options are relatively  
2 limited.

3 Some people would include some of the  
4 class 1A agents in this category, others would not.  
5 But I think most people would agree that the 1C drugs  
6 are contraindicated in these subsets.

7 And in thinking about where Dofetilide  
8 might provide an additional option, while it shows  
9 efficacy in all three categories of patients, perhaps  
10 the most crying need, in terms of an additional agent,  
11 are in the groups of patients with advance structural  
12 heart disease.

13 In summary, then, maintenance of normal  
14 sinus rhythm is a necessary goal in some patients with  
15 symptomatic atrial fibrillation in whom the symptoms  
16 are due to the presence of AF, that is the loss of  
17 atrial transport.

18 Our current therapeutic options,  
19 particularly in patients with advanced structural  
20 heart disease are limited, and all of them are  
21 associated with measurable risk.

22 Dofetilide is effective in the conversion

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1 of atrial fibrillation, and in the maintenance of  
2 normal sinus rhythm, to an extent that is comparable  
3 to that seen with other currently used agents for the  
4 treatment of this problem, and the drug is well  
5 tolerated.

6 The risk of Dofetilide is proarrhythmia, as  
7 it is with most other antiarrhythmic agents, and in  
8 this case specifically Torsade de points. And as you  
9 have heard, both the occurrence and the consequences  
10 of Torsade can be minimized with the use of the  
11 proposed treatment algorithm, and in hospital  
12 initiation.

13 And I would reemphasize that these two  
14 features constitute a critical cornerstone to the safe  
15 and appropriate use of this drug.

16 Finally, there is no evidence to suggest  
17 a mortality risk in patients with advanced structural  
18 heart disease treated with Dofetilide, and with the  
19 exception of Amiodarone, these are data that do not  
20 exist for any other antiarrhythmic drug that is  
21 currently being used.

22 As a result of the foregoing, Dofetilide

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1 would provide a useful addition to our pharmacologic  
2 armamentarium for the treatment of patients with  
3 symptomatic atrial fibrillation.

4 Thank you.

5 ACTING CHAIRMAN CALIFF: Well, let me  
6 suggest that we take a break for lunch, and that we  
7 come back and have Pfizer identify a captain of the  
8 team to preside, because I know there are many  
9 consultants who may be called on in the discussion.

10 If we could reconvene, then at 1:15?

11 (Whereupon, at 12:53 p.m. the above-  
12 entitled matter was recessed for lunch.)

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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (1:30 p.m.)

3 ACTING CHAIRMAN CALIFF: I want to thank  
4 the people for making a valiant effort here to get  
5 through lunch. Probably a fair amount of indigestion  
6 in the crowd.

7 What I think would be most effective would  
8 be to now launch into the questions, and if the  
9 Sponsor has a team captain who wants to come up to the  
10 podium?

11 There is a lot of material that we've been  
12 through, and a lot of issues. It would be fun,  
13 actually, to spend a couple of days just discussing  
14 the issues around atrial fibrillation, and all the  
15 implications that this data brings up, but we  
16 obviously have a different job to get done today.

17 So what I would like to do is start with  
18 our two primary reviewers, and then go to Ralph  
19 D'Agostino to ask whatever questions you have about  
20 the data that has been presented.

21 DR. GRINES: I have a series of questions  
22 related to the last two talks that were done.

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1 My first question relates to the 14 day  
2 run in period, and exactly what was done during that  
3 14 day period?

4 DR. RYDER: The 14 day run in period? Dr.  
5 Friedrich?

6 DR. FRIEDRICH: This was -- I take it you  
7 refer to the studies 345 by a running period of 14  
8 days?

9 DR. GRINES: Yes.

10 DR. FRIEDRICH: Was in place. During that  
11 period patients who were not anticoagulated were  
12 anticoagulated, and also it was established that they  
13 were in atrial fibrillation, so an EKG was done, and  
14 the patients were in atrial fibrillation that had  
15 least passed this entry criteria.

16 But mainly, the main reason is that  
17 patients were anticoagulated, and if local practice  
18 was such that you would have a longer period of  
19 anticoagulation, then that was done.

20 DR. GRINES: Additional questions that I  
21 have relate to the proportion of patients who can  
22 actually start the trial, and that finish it. And,

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1 for example, in the 345 and 120 studies, patients were  
2 enrolled acutely, and then if they cardioverted,  
3 either by drug, or by electrocardioversions, they went  
4 on to the maintenance phase.

5 And I would like you to go through,  
6 perhaps, a hypothetical 100 patients that were  
7 enrolled and tell me how many of them ultimately were  
8 cardioverted if one adds electricity to the drug, did  
9 the drug increase the cardioversion success rate?  
10 That is my first question.

11 And then secondly how many of them were  
12 able to continue on the drug for the one year follow  
13 up period.

14 DR. RYDER: I believe that Dr. Friedrich  
15 has the specific data from the clinical trials.

16 DR. FRIEDRICH: In both studies 345 and  
17 120, the two studies that I have shown you, those  
18 patients that did not convert pharmacologically were  
19 cardioverted, as I have shown. This is -- in  
20 different treatment group it was a little bit  
21 different, but on average 20 percent of patients that  
22 were enrolled into this conversion phase did not

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1 convert either pharmacologically, or when a  
2 cardioversion attempt was made.

3 So on average about 20 percent of patients  
4 did not get in sinus rhythm, and was stopped at that  
5 time.

6 DR. GRINES: Did the drug enhance the  
7 ability to be cardioverted? Say, for example, if I  
8 have a patient with atrial fibrillation, and I want  
9 them cardioverted, the question is, should I spend  
10 three days worrying about this patient, or should I  
11 just electrically cardiovert them? Does this drug add  
12 anything to my cardioversion?

13 DR. FRIEDRICH: We have not specifically  
14 designed a study to look, for instance, if different  
15 protocols of DC cardioversion would be more effective  
16 with Dofetilide on board, or not on board. So we  
17 can't answer this question.

18 DR. GRINES: But you know the proportion  
19 of patients in the placebo group, and the treatment  
20 group that were ultimately successfully cardioverted,  
21 correct?

22 DR. FRIEDRICH: And that was no different.

1 DR. GRINES: No different, okay.

2 DR. FRIEDRICH: In essence 80 percent of  
3 the patients that entered the trial made it into the  
4 maintenance phase.

5 DR. RYDER: I believe that the difference  
6 was restricted to the 30 percent that got  
7 pharmacologically converted in the Dofetilide 500  
8 microgram BID group, compared to very few in the other  
9 dose groups, and very few in placebo.

10 DR. GRINES: Right, that was clear, but  
11 from a clinician standpoint we won't just stop at  
12 administering -- if we are bent on cardioverting  
13 somebody we are going to add electrical cardioversion.

14 And so then, from my standpoint the  
15 ultimate success rate does not differ depending on  
16 whether they are treated or not.

17 DR. FRIEDRICH: What you say, basically,  
18 is these 30 percent that pharmacologically convert,  
19 these patients do not need to undergo electrical  
20 cardioversion, that is the net result, really.

21 But, I mean, if you take 100 patients, 20  
22 percent of these patients, or 20 patients, would not

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1 be cardioverted by either pharmacological or  
2 electrical means, and at least 30 percent of these 100  
3 patients that pharmacologically convert, and 50  
4 percent that would need to be cardioverted.

5 DR. GRINES: So once they are started into  
6 the maintenance phase then how many of them either  
7 drop out or ultimately go back into atrial  
8 fibrillation?

9 DR. FRIEDRICH: I best show you the  
10 Kaplan-Meier curve again, because that is the answer  
11 right there, if I may. Efficacy core slide number 13,  
12 please.

13 This curves show the probability of  
14 remaining in normal sinus rhythm for different  
15 treatment groups, starting from the top 500 microgram  
16 BID Dofetilide, 250 the next line, 250 microgram BID,  
17 the green line Sotalolol, and below that 125 microgram  
18 BID Dofetilide.

19 So you can estimate how many patients stay  
20 throughout the trail in sinus rhythm through the end  
21 of the trial. So if you go across you see about 70  
22 percent of patients on 500 microgram BID in normal

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1 sinus rhythm at the end of the trial.

2 DR. GRINES: Am I supposed to be looking  
3 at the curves, or those numbers?

4 DR. FRIEDRICH: At the curves.

5 DR. GRINES: But the numbers at the bottom  
6 say that your sample size is only 31 patients at 12  
7 months. What does that number represent? Below the  
8 12?

9 DR. FRIEDRICH: That is the actual number  
10 of patients still in the trial at this point.

11 DR. GRINES: See, that was my question.

12 DR. FRIEDRICH: The curves give you a  
13 probability.

14 DR. GRINES: Yes, that was my question,  
15 how many patients are -- say, for example, if you have  
16 100 patients how many are cardioverted, can continue  
17 on the maintenance, and at 12 months are still on the  
18 drug?

19 DR. FRIEDRICH: It is right there,  
20 compared to the placebo group it is 31 patients on  
21 Dofetilide versus 7 patients on placebo.

22 DR. GRINES: So out of 100 patients --

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1 now, this is a different question. Out of 100  
2 patients who successfully converted only 31 remain on  
3 drug at 12 months, is that correct?

4 DR. RYDER: Do you have the slide showing  
5 the proportion of patients discontinued during the  
6 trial, and for the various reasons?

7 DR. FRIEDRICH: Backup slide number 19.  
8 This slide is from study 345, it shows you  
9 discontinuations related to study drug, split up by  
10 the different treatment groups, Dofetilide 125, 250,  
11 500, Sotalol and placebo.

12 On the top you see the number of patients  
13 randomized. Total discontinuations is the yellow  
14 line, during the course of the trial.

15 DR. GRINES: But these numbers look  
16 different than -- this is randomization at the  
17 beginning?

18 DR. FRIEDRICH: That is correct.

19 DR. GRINES: Prior to cardioversion?

20 DR. FRIEDRICH: Was that your question?  
21 I mean, how many patients entered the trial, in other  
22 words were randomized, and then were discontinued

1 during the trial?

2 DR. TEMPLE: That doesn't include for  
3 failure.

4 DR. FRIEDRICH: This doesn't include  
5 relapse, this is discontinuations.

6 DR. GRINES: So basically 30 percent might  
7 be discontinued due to a drug side effect, and then  
8 another 40 percent might have relapse and atrial  
9 fibrillation?

10 DR. RYDER: No, I think that is misreading  
11 the slide. The number is for 500 micrograms BID, the  
12 first yellow line is the total number of patients  
13 discontinued, and then that is segregated below, and  
14 on the following slide, it is continued, so that that  
15 number will be 6, plus 7, plus 2, if you could show  
16 the following slide.

17 DR. TEMPLE: But that does not include  
18 people who discontinued because they failed?

19 DR. FRIEDRICH: That is correct. That  
20 information you get from the Kaplan-Meier curve,  
21 because that shows you exactly how many questions --

22 DR. TEMPLE: Yes, but that is the question

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1 Dr. Grines is asking, at 12 months, for all the  
2 reasons that people left, how many are still in normal  
3 sinus rhythm at the end?

4 DR. FRIEDRICH: That is in the Kaplan-  
5 Meier curve, so if we could go back to --

6 DR. GRINES: So out of 100 patients that  
7 entered the maintenance phase, only 30 of them are  
8 going to be taking the drug in sinus rhythm at 12  
9 months?

10 DR. RYDER: To get to the real heart of  
11 the matter, no pun intended, I would like to ask Glen  
12 Andrews, who is the statistician who actually ran the  
13 Kaplan-Meier curve to speak to the issue.

14 DR. ANDREWS: Essentially I would like to  
15 draw your attention to the briefing document, table 12  
16 of the briefing document which deals with this in a  
17 bit of detail.

18 There are, essentially, a couple of  
19 issues, really, although 12 months was the specified  
20 end of the study, some investigators chose to have  
21 their patients come in prior to 12 months, and there  
22 was a two week window specified in the protocol.

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1           So the 31 patients you see for the 500  
2 group are those that made it to 12 months in total.  
3 In the briefing document in table 12, then, the number  
4 completing the study is 49, so it is approximately 50  
5 percent.

6           DR. FRIEDRICH: Can I make one more point?  
7 Those discontinuations that occurred because patients  
8 relapsed were protocol driven, of course, because a  
9 patient who relapsed, the study -- the protocol  
10 prescribed that these patients were discontinued.

11           In the real world you would probably go on  
12 with these patients. I will ask Dr. Ruskin to talk to  
13 that issue, what really happens in atrial fibrillation  
14 treatment when you consider patients that are in need  
15 of treatment.

16           DR. GRINES: Another -- did you want to  
17 say something?

18           DR. RUSKIN: I just wanted to make one  
19 brief comment, and that is if we could look at the  
20 primary analysis for 345, the Kaplan-Meier curves,  
21 because another way to look at this, in terms -- I  
22 think you are getting at a practical question, which

1 is, what is the clinical impact here.

2 Another way to look at it is what is the  
3 median time to recurrence. And on that curve you can  
4 see that on 500 BID, even out to a year, you haven't  
5 hit 50 percent recurrence rate, whereas on placebo  
6 you've got a median type to recurrence of about a  
7 month.

8 So another way of thinking about it is  
9 that if you are on the drug, your chances -- if you  
10 are maintained on the drug, your median time to 50  
11 percent, or time to 50 percent recurrence is more than  
12 a year, versus one month off therapy.

13 In this protocol people were dropped out  
14 if they had a single recurrence at anywhere along that  
15 route. And from a clinical perspective, I think that  
16 most of us would agree that if a patient went six  
17 months on a drug without a recurrence, had a  
18 recurrence at six months, we would probably  
19 cardioverted discontinue to treat them, and there is  
20 no way to evaluate that from this trial, which is not  
21 designed to look at things that way.

22 DR. GRINES: Well, the reason I bring it

1 up isn't because of the efficacy question, it is more  
2 related to the safety issue. And if we only have a  
3 proportion, and my calculation about 40 percent of the  
4 patients completed this study on a particular drug  
5 regimen, then how sure are we of its safety analysis?

6 You know, unfortunately all the safety  
7 data that was given to us incorporated these very low  
8 doses which, presumably, will not be marketed.

9 And if one looks at the number of patients  
10 who actually received the 500 BID it is only about a,  
11 I think we calculated here about 106 patients in the  
12 total -- in the 345 and the 120.

13 And although a lot of emphasis was placed  
14 on the Diamond study, they received a half dose, they  
15 received 250 twice a day for atrial fibrillation. Is  
16 that correct?

17 DR. RYDER: That is correct, but I think  
18 there is an important point that I don't want the  
19 committee to miss, and that is, there is no dose of  
20 Dofetilide. Dofetilide is a treatment regimen, and  
21 the dose that you are administered from the inception  
22 onward is dependent upon your creatinine clearance.

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1           And so the randomized dose group that was  
2 shown you received 500 micrograms BID or a lower dose  
3 specified according to their creatinine clearance.  
4 And the intent was to get a common systemic exposure.

5           And the specific analysis that Dr. Pratt  
6 referred to, was one where he had us go into the data  
7 base and say, after this learning was obtained, during  
8 the clinical program in early 1994, and you realized  
9 that you should down-titrate, or administer, I should  
10 correct myself, administer from day one a lower dose  
11 if your clearance of creatinine is less, what does the  
12 safety look like in patients who would be getting the  
13 recommended regimen?

14           And that is what Dr. Pratt presented.

15           DR. GRINES: Right, but according to our  
16 calculations, and actually it is data from your slide  
17 number 24, if one combines the 345 and 120 studies,  
18 that is only 157 patients who received either the 500  
19 dose, or the reduced dose for creatinine clearance.

20           DR. RYDER: From the two pivotal trials I  
21 think that that is correct. But I would offer the  
22 committee that I think that to dismiss safety data

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1 from other patients, for example, take Diamond AF.  
2 Patients who are in Diamond AF were typically in their  
3 70s, they had lower creatinine clearances, and they  
4 were receiving 250 micrograms BID.

5 Today, if we were to administer Dofetilide  
6 the way we were going to recommend it, if their  
7 creatinine clearance was less than 60, that is what we  
8 would say to start them on, 250 micrograms BID.

9 So I would offer the committee that that  
10 data may be relevant, and that is what Dr. Pratt  
11 included -- had us include in his analysis.

12 DR. GRINES: But how many additional  
13 patients would that be, would have been treated at the  
14 recommended dose?

15 DR. PRATT: You are referring now, Dr.  
16 Grines, to the Diamond AF study?

17 DR. GRINES: Right, the Diamond atrial  
18 fibrillation.

19 DR. PRATT: So let's go to backup 35  
20 please. That is safety backup 35, please. And there  
21 is your answer, all but 85 of Dofetilide assigned  
22 patients would have received that.

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1           Now, the question of safety then, might be  
2 best asked -- by the way, the overall analysis that I  
3 showed you after the algorithm included all those  
4 patients below that 85, okay? So they were included  
5 in the analysis that I showed you on my -- on your  
6 slides, about 38, 39 and 40.

7           But if we go to the next one, backup 36 --

8           DR. GRINES:     So you have 100 extra  
9 patients here?

10          DR. PRATT: No, go back please, go back to  
11 35. We have 85 from 249. So we have about 160.

12          DR. GRINES:     So that was a protocol  
13 amendment to drop the dose? Because it was my --  
14 maybe I missed something in the presentation.

15          DR. PRATT: Let me go back, because a  
16 decision was made by the sponsor in this trial to  
17 treat all patients with this sever LV systolic  
18 dysfunction with 250 micrograms BID as the maximum  
19 dose they would give, a decision made years ago.

20                 It was a decision made even before the  
21 algorithm was initiated. What we did was to go back  
22 and say, were all these 249 to be put in a trial now,

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1       how would we treat them? And the answer is, all but  
2       85 would have received 250 or less, based on the renal  
3       algorithm.

4               Now, I can show you the safety data  
5       associated with that, that is in backup 36. And  
6       backup 36 says that they look pretty much the same in  
7       terms of mortality, as all the patients did.

8               So we've eliminated those 85 because they  
9       would have received 500 BID, and we can never guess,  
10      or intimate what they might have done.

11              So that was our closest approximation of  
12      that very good question.

13              ACTING CHAIRMAN CALIFF: Bob, you had a  
14      comment on this issue, or a question?

15              DR. TEMPLE: Yes, I guess my question  
16      would be why would only the people with AF from the  
17      Diamond study be relevant? Wee are interested in  
18      whether the people are susceptible to Torsade.

19              So you might also have people from the  
20      rest of the trial who at least are relevant, in some  
21      way, to the question. It is not just the people with  
22      AF.

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1 DR. PRATT: Absolutely, and Dr. Temple,  
2 we've shown that analysis in that everybody else in  
3 Diamond was randomized to 500 BID until the  
4 implementation of the renal algorithm. That is why  
5 the Torsade rate was quite high.

6 I showed you that before and after, and it  
7 is in your document, where we really go down in  
8 Diamond MI, for instance, from 2,9 to 0.8 percent  
9 using the algorithm.

10 So there was a learning curve in how to  
11 use this drug, or if you will, how to not use it, and  
12 those were corrected, and all those patients are  
13 included, all the patients randomized after 500 are  
14 included in that analysis that begins on slide 38.

15 Would you like me to go through a little  
16 more detailed version of that? I think maybe it is  
17 pretty important, it is the real life use of this  
18 drug.

19 Dr. Grines pointed out something very  
20 important, that is that when we first developed a look  
21 at things we were certainly combining pre and post-  
22 algorithm, such as this kind of slide.



1           So the idea was to make a more detailed  
2           analysis, and that starts on core slide 38. And that  
3           includes all the patients to the right of that  
4           vertical line, all the patients in the SVA trials, the  
5           ten trials, to document a safety, and the Diamond  
6           trials, every patient, Dr. Temple, in those trials.

7           And if we could go then, to safety backup  
8           3. And those are the actual numbers of the people  
9           that are in the trial, that were appropriately dosed  
10          according to the algorithm that is being proposed.

11          And that is, we have a total Dofetilide  
12          and placebo, of about 33, or nearly 3,400 patients,  
13          and they include 900 patients in the SVA trial.

14          So these are all dosed at 500 at  
15          randomization.

16          ACTING CHAIRMAN CALIFF: Marv, you had a  
17          question about --

18          DR. KONSTAM: Craig, can I just follow on  
19          that?

20          DR. PRATT: Yes. Unfortunately I'm sort  
21          of in a hole here, but I hear you.

22          DR. KONSTAM: But with the Diamond AF you

1 started automatically at a lower dose, right? In the  
2 Diamond trial with the AF patients?

3 DR. PRATT: Right. So we included in this  
4 analysis, at Diamond AF, are just the 139 Dofetilide,  
5 and 135 placebo assigned patients whose creatinine  
6 clearance was less than 60, so they would have  
7 received 250 BID or less.

8 DR. KONSTAM: Well, just clarify that a  
9 bit more. If you had a normal creatinine clearance,  
10 and you were in Diamond AF --

11 DR. PRATT: You are one of those 85 that  
12 would not be included here.

13 DR. KONSTAM: Okay, but then if you had --  
14 if you were in Diamond AF and you had a low creatinine  
15 clearance, and you were randomized to the 500 group,  
16 what dose did you wind up getting?

17 DR. PRATT: Could you repeat it? I'm  
18 sorry.

19 DR. KONSTAM: Well, I think it needs a  
20 little clarification so that -- the AF patients in  
21 Diamond automatically started at 250 BID?

22 DR. PRATT: And that was true even before

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1 the algorithm.

2 DR. KONSTAM: Right, so if somebody had AF  
3 in Diamond, and they had a low -- I guess it is less  
4 than 60 creatinine clearance, what was their dose?

5 DR. PRATT: Before the algorithm it was  
6 250, after the algorithm it was 250 or less.

7 DR. RYDER: It was less if they were -- if  
8 they had a creatinine clearance less than 40, which  
9 was the next categorical change in dosing. The  
10 recommended dosing is, if your creatinine clearance is  
11 greater than 60, 500; 40 to 60, 250; 20 to 40, 125;  
12 and that is from the first dose on.

13 The next change, the only other adjustment  
14 that is allowed is after the first dose, in order to  
15 asses individual pharmacodynamic responsivity, QTc is  
16 looked at, after the first dose, two to three hours  
17 after the first dose, if it is greater than 500, or  
18 greater than a 15 percent change from baseline, we are  
19 conservative, whichever criteria is met, then the dose  
20 is lowered.

21 No other adjustments are allowed for QTc.  
22 The threshold that then comes into play is

1 discontinuation. And that would be if you have a 500  
2 millisecond absolute value after that period of time  
3 you are discontinued from the trial.

4 And the reason for the dose adjustment  
5 after the first dose is that the reason for dose  
6 adjusting is to try to get the best efficacy but limit  
7 Torsade. And Torsade is an event that in our data set  
8 mostly happened early on.

9 And so the dose adjustment is after the  
10 first dose. And when you do that adjustment, that is  
11 the analysis, this all pertains to the analysis that  
12 Dr. Pratt has.

13 DR. PRATT: Dr. Califf, I didn't quite get  
14 to finish the extra data I was going to show, we kind  
15 of got sidetracked by who they were, so --

16 ACTING CHAIRMAN CALIFF: Would it be  
17 helpful?

18 DR. PRATT: I think it will.

19 ACTING CHAIRMAN CALIFF: Okay.

20 DR. PRATT: I believe so. Could we put  
21 backup slide 3 back up there?

22 This is, again, the 500 BID real life

1 doses. So if we could go to backup 5 now, this is one  
2 analysis that you didn't see. You see there is no  
3 mortality signal, and this is across the board for  
4 both males and females, dosed according to the  
5 algorithm, 500 BID, for men and women across all the  
6 trials.

7 And there is the point estimates and  
8 mortality given in a way that we recommend giving it.

9 ACTING CHAIRMAN CALIFF: I think Dr.  
10 Lipicky and Dr. Temple both had comments.

11 DR. LIPICKY: I'm not sure I followed the  
12 discussion. What are you trying to figure out?

13 DR. GRINES: Well, I was trying to figure  
14 out whether we had an adequate safety profile based on  
15 the recommended dose.

16 DR. LIPICKY: Based in what, in patients  
17 with AF?

18 DR. GRINES: That was what I was initially  
19 driving at, if we are approving it for atrial  
20 fibrillation --

21 DR. LIPICKY: Well, we purposely advised  
22 the company, and maybe we shouldn't have, and maybe

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1 that is the issue, that all of their experience is  
2 pertinent to the safety data base.

3 And that all of the patients that have  
4 received Dofetilide, including those patients that  
5 have structural heart disease who do not have atrial  
6 fibrillation, is pertinent to their data base.

7 DR. GRINES: Right.

8 DR. LIPICKY: So that -- I mean, that  
9 notion can be rejected, but --

10 DR. GRINES: No, I think that is a good  
11 notion, I just was not entirely clear about how many  
12 patients we had with 500 BID dose.

13 DR. LIPICKY: In AF?

14 DR. GRINES: Or in the entire data set.

15 DR. LIPICKY: Well, that would be a good  
16 question.

17 DR. GRINES: Well, that would be a good  
18 question. But then there is a second part of that  
19 question, I guess, and that is, at least at the moment  
20 there is no foregone conclusion that 500 milligrams is  
21 the only dose that will be recommend.

22 I don't know, nobody has said that yet.

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1                   ACTING CHAIRMAN CALIFF: He said it, and  
2 I think we will get back to it.

3                   DR. LIPICKY: Well, we don't care what he  
4 said.

5                   (General laughter.)

6                   ACTING CHAIRMAN CALIFF: This part of the  
7 discussion, I think, was important to almost everyone  
8 around the panel because things changed during the  
9 development course, and it wasn't clear how many  
10 patients were in which part. But I think that has  
11 been clarified now.

12                  DR. TEMPLE: What I heard, and maybe this  
13 is going to be redundant, but as to the number of  
14 people with AF who got the 500 dose, what we've been  
15 told is that in addition to the obvious ones from the  
16 two trials in AF, there is another 150 people who  
17 should be counted that way, because if they had been  
18 meant to be given the 500 dose they would have been  
19 reduced to 250 because of their creatinine clearance.

20                  And then there is other people who didn't  
21 have AF who got 500 in other trials.

22                  ACTING CHAIRMAN CALIFF: So, anyway, are

1       there more questions?

2                   DR. PRATT: Cindy, just one last fact that  
3       may help, and that is, that in the Diamond AF  
4       population that would have been included in this  
5       analysis, 128 of those were followed at least for one  
6       year.

7                   ACTING CHAIRMAN CALIFF: Peter?

8                   DR. KOWEY: Jeremy, would you or Craig  
9       like to tell us why you think this drug doesn't work  
10      for paroxysmal fibrillators? And the reason I bring  
11      this up is because again my concern, and I think Tom's  
12      concern earlier was, we are concerned about  
13      practitioners. Practitioners are not used to thinking  
14      about drugs for AF working for some AF and not all AF.  
15      And it doesn't work for PAF.

16                   First of all, do you think that is true,  
17      what I just said? And, secondly, if it is true, then  
18      why do you think it is true?

19                   DR. RUSKIN: Well, I don't disagree with  
20      your statement, the short answer is I don't know why  
21      it doesn't work in PAF, and certainly the lack of a  
22      clear benefit in those populations is perplexing, and

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1 persistent atrial fibrillation who are converted.  
2 That is the information.

3 ACTING CHAIRMAN CALIFF: Just a point of  
4 clarification, Peter, since you asked the question.  
5 Are you saying that you regard the data that was in  
6 the submission to be definitive that the drug doesn't  
7 work, or do you think the studies were adequate and  
8 prove that the drug does not work in paroxysmal atrial  
9 fibrillation?

10 DR. KOWEY: Yes.

11 ACTING CHAIRMAN CALIFF: Would it be fair  
12 to ask the sponsor if that is their conclusion?

13 DR. KOWEY: I asked Jeremy, I didn't ask  
14 the sponsor, I guess we can do that.

15 DR. RYDER: I think that there are some  
16 potential design issues, but it is hypothetical, but  
17 the fact is that there are no data to show that  
18 Dofetilide works in PAF, and it is not a claim in the  
19 data, it should be laid out.

20 DR. KOWEY: My next question, Craig, you  
21 mentioned, and I don't know whether you have a slide  
22 to show us, one of the questions we are going to get

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1 asked about is using the drug in patients with  
2 ischemia, and you mentioned it, I know that you went  
3 over it, probably because you saw the question.

4 Do you have a slide to show us on that, or  
5 some way of showing us the data?

6 DR. PRATT: Well, I have the data. What  
7 I did, first of all, could we put back safety core  
8 slide 14, please?

9 Peter, I guess the first thing is, when  
10 we've been on the committee, and when guidelines have  
11 been established, there has been a lot of requests in  
12 the guidelines for more patients with structural heart  
13 disease. There they are, right there, Diamond CHF and  
14 Diamond MI.

15 In terms of ischemia, I just call your  
16 attention to the right. I mean, there is no signal  
17 there in an early MI population. And what we did, for  
18 both populations, is we took all those patients that  
19 had, on one of their case report forms, angina,  
20 checked yes.

21 And, of course, that was war, that was --  
22 let's see, 488 in Diamond MI and 325 in Diamond CHF.

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1 They are equally distributed for baseline risk  
2 factors, and they are equally distributed between the  
3 two groups, and the relative risk of being on  
4 Dofetilide in Diamond CHF is 0.98, and the relative  
5 risk in Diamond MI is 0.84. And we would have liked  
6 to have had that kind of information in a lot of  
7 trials.

8 DR. KOWEY: I thought that is what you  
9 said. I wasn't disagreeing with you, I just wanted to  
10 hear you give us the numbers again, because we didn't  
11 have a slide.

12 DR. PRATT: Well, I went over it very  
13 quickly, and I apologize.

14 DR. KOWEY: That is fine. Do you know  
15 what the Torsade rate was in 345 in the sotalol arm?

16 DR. PRATT: There were zero cases. On 80  
17 BID of Sotalol.

18 DR. KOWEY: Can you give us some idea, I  
19 would like to explore a little bit the 750 milligram  
20 dose, and the fact that it was used for a while, and  
21 then it was dropped, for obvious reasons, there was a  
22 high Torsade rate in that population.

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1 Do you have any data on blood levels and  
2 QT data in that experience of the 750 milligram  
3 patients?

4 DR. PRATT: Steve, you might --

5 DR. RYDER: I think that the clinical  
6 pharmacology group, I would ask them to comment on  
7 this, because I believe that higher doses, even above  
8 750 micrograms BID up to, I believe, 1,250 micrograms  
9 BID was administered in the clinical pharmacology  
10 trials.

11 And perhaps maybe Don Nichols would field  
12 that question. Yes, but he needs to come up and use  
13 the mike. And while he is doing it, I just remind  
14 you, in the clinical trials there were 908 normal  
15 subjects with doses up to 1,250 BID and zero Torsade.

16 DR. KOWEY: I wasn't concerned about the  
17 Torsade as much as I was concerned about looking at  
18 blood levels and QT data.

19 DR. PRATT: And now I'm sitting here as  
20 the microphone holder, waiting for somebody to come  
21 up.

22 MR. NICHOLS: You may be talking about

1 something different than I'm thinking about, but in  
2 core slide 19, clinical pharmacology core slide 19.

3 This is this graph of the change in  
4 sensitivity over time. But these are doses of 750  
5 micrograms -- I'm sorry, 1 milligram twice a day. So,  
6 again, that is why that bar, that white bar going  
7 across there is where 500 twice a day puts you, and  
8 you see that those levels to the far right are, you  
9 know, around twice that, and that is why, this is  
10 twice as big a dose. These are healthy volunteers.

11 DR. KOWEY: That helps, thank you. I  
12 think I have one more question. The way this drug is  
13 going to be used is in a way that is not similar to  
14 the way we -- I think I said this earlier, similar use  
15 the antiarrhythmic drugs today.

16 Let's say, for example, a patient is  
17 assigned to a dose based on creatinine clearance, and  
18 they are dosed with that drug dose, and they don't  
19 have a QT prolongating effect, and they don't convert  
20 their arrhythmia.

21 Is there any experience with titrating  
22 upwards on the dose? There is absolutely no experience

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1 doing that?

2 DR. RYDER: That dose regimen was not  
3 explored, upward titration.

4 DR. KOWEY: It has never been done in the  
5 history of creation?

6 DR. RYDER: With Dofetilide it was not  
7 done in the clinical program.

8 DR. KOWEY: Because it brings up another  
9 labeling issue, because the response the physicians  
10 will have, again I'm acting like a country doctor, I  
11 don't know why I'm doing this today, but the reaction  
12 that doctors are going have is, if I gave the drug at  
13 a dose that I thought was a reasonable dose based on  
14 whatever it is that I calculated, and it doesn't work,  
15 and it doesn't prolong the QT interval, then maybe I  
16 will just use a higher dose.

17 And so we have to make sure we tell them  
18 not to do that, correct? Because we have no data to  
19 support doing that, right? What do you think?

20 DR. LIPICKY: Did you ask me, or --

21 DR. KOWEY: Yes, I was asking you.

22 DR. LIPICKY: I don't think I would say

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1 that, what you just said. I will grant you there is  
2 no empirical information that says it works, but I  
3 think the properties of the drug have been well laid  
4 out, and that just because someone did not empirically  
5 verify that that works, I think I understand the  
6 properties of the drug.

7 DR. KOWEY: I'm confused. So you would  
8 tell people that it is okay?

9 DR. LIPICKY: I would not tell them they  
10 cannot. And if someone elected to, I would not put  
11 into writing, if thou doest this, thou are not.

12 (General laughter.)

13 DR. KOWEY: I wouldn't recommend putting  
14 thou in the package, I don't think that is ever a good  
15 idea.

16 DR. LIPICKY: And I don't think that would  
17 necessarily be inappropriate use of the drug, given  
18 what you know about it. I would not advise, I would  
19 not recommend it be done by saying this is an option.

20 ACTING CHAIRMAN CALIFF: Bob has a comment  
21 on that.

22 DR. KOWEY: I just want to make sure this

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1 is being taped, so we have this for posterity.

2 DR. TEMPLE: But the point is, we are  
3 asking you questions like that, and it is very nice  
4 that you asked Ray, also, but if you reach the  
5 conclusion, you collectively, that the lack of empiric  
6 information about using it that way is a reason not  
7 to, you need to tell us that, and then we need to  
8 figure out -- I guess I want to say this for most of  
9 the discussion.

10 There is a million options here, and it is  
11 almost hard to talk about anything without thinking of  
12 them. But as you think about each of the things that  
13 concern you, consider whether that concern is so  
14 overwhelming that, you know, you have a negative view,  
15 or whether there is something that the company could  
16 try to do to solve that problem.

17 Well, some things are obvious, you put  
18 stuff in the label. Other things are less obvious. I  
19 just want to remind you of this. One of the concerns  
20 with the use of Tamoxiphen to reduce the risk of  
21 breast cancer is that physicians would not know how to  
22 calculate what is called the Gayle score, which is how

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1 you calculate the risk of breast cancer.

2 The company is providing a little  
3 calculator. Well, I forget, they are either providing  
4 a calculator, or they have the website that has the  
5 calculator on it, so that everybody can calculate the  
6 Gayle score.

7 Well, you could do that with creatinine  
8 clearance, it was a surprise to me to hear that nobody  
9 knows how to do that. But there are things that one  
10 could think of that would make that possible, whether  
11 those will be material to you or not, you all have to  
12 figure out.

13 But there is a lot of possibilities. You  
14 can even imagine registering people at the time they  
15 get into a hospital, and not allowing people to get  
16 drug unless they've been through a hospital, in case  
17 you are worried about people slapping folks on the  
18 drug without going through the hospital phase.

19 There is a lot of things to think about  
20 that may or may not be relevant to you, and this is  
21 one of them. Ray thinks, what the heck, go try it.  
22 You are in a hospital, if you get Torsade they will

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1 bail you out. Someone else might think it is not  
2 worth it, you don't know if you can bail people out  
3 under those circumstances.

4 So you are free, and we are asking you to  
5 think about all of those possibilities as we go on.

6 DR. GRABOYS: Let me just go through  
7 another possible scenario. Pete, you said, if there  
8 was breakthrough, and I think Jeremy said then you  
9 would just go up on the dose. No?

10 DR. RYDER: No.

11 DR. GRABOYS: No one said they would go up  
12 in the dose. Is there any experience that a patient  
13 reverts to atrial fibrillation and has been on 250  
14 twice a day, and now gets 500 in an attempt to augment  
15 that?

16 DR. RYDER: No.

17 DR. GRABOYS: Do you have any data on  
18 that?

19 DR. RYDER: No.

20 ACTING CHAIRMAN CALIFF: Peter, any  
21 further questions? If we could just -- there were two  
22 things that were said that I think might deserve some

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1 comment, because there are bunches of frameworks of  
2 reference that can be brought to bear, and I want to  
3 introduce one.

4 And that is, this word maintenance implies  
5 that people can break through, okay? There is another  
6 framework of reference, that is that if you have  
7 atrial fibrillation it will always come back, and that  
8 all you do with the drug is to increase the duration  
9 of time before it does.

10 Now, that is a different framework of  
11 reference, it doesn't say there is breakthrough, it  
12 doesn't say the drug failed, can you make it work  
13 again. It says that the time to recurrence gets  
14 longer.

15 And I ask you to think about that  
16 framework of reference as you talk about things, as  
17 opposed to it breaks through because it failed. So  
18 that is thought one.

19 Thought two is I was willing to have the  
20 sponsor bring the PSVT trials here, and argue that  
21 they work. And I would have supported that notion.  
22 So I don't think the trials that exist prove it does

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1 not. That is just one other person's opinion, and  
2 that was a question.

3 I don't think we know it does not work in  
4 PSVT. It doesn't look real promising, I admit that.  
5 But I don't think we really know it does not work.  
6 There is nice dose related stuff all through all those  
7 trials.

8 DR. LIPICKY: Are you talking about PSVT  
9 or PAF, or both?

10 ACTING CHAIRMAN CALIFF: Fine. I'm sorry,  
11 I don't know what I'm talking about.

12 (General laughter.)

13 ACTING CHAIRMAN CALIFF: It is the  
14 conglomerate data for the paroxysmal tachycardia.

15 DR. KOWEY: Including AF?

16 ACTING CHAIRMAN CALIFF: Including AF.

17 DR. KOWEY: I don't think I totally  
18 disagree with what you just said. But I think for the  
19 purposes of the discussion today, whatever it is that  
20 you did say, I would be happy to explain what you said  
21 later.

22 I think that you are right, there maybe --

1 there is a signal, perhaps, that there is some  
2 efficacy. But I think for the purposes of what we are  
3 going to discuss today, it ain't there.

4 ACTING CHAIRMAN CALIFF: I'd like to give  
5 Ralph a chance to bring up any statistical, or  
6 clinical issues that are of interest.

7 DR. D'AGOSTINO: In the vein of country  
8 documents, I'm a country statistician from Boston, and  
9 I have just a couple of rules that I sort of look  
10 like, sort of lay down, willing to bend them as we go  
11 along.

12 But I tend to, in these settings, say do  
13 we have two studies, are they reproducible, were the  
14 analysis that were laid out in the protocol  
15 implemented, and did the results come from two  
16 confirmatory trials?

17 Now we don't have that here. There is the  
18 study 345, which is quite substantial, and the study  
19 120, which is being discussed as a sort of support, or  
20 what have you.

21 And it means a lot to me to understand why  
22 120 isn't saying the same, or is it saying the same,

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1 and what is it saying.

2 120 doesn't have the dose response. If  
3 you look at 345, it looks like the 250 dose, and the  
4 500 dose are almost the same. If you look at 120, the  
5 study 120, it looks like the dose 500 and 250  
6 numerical differ. And 250 looks like 125.

7 So I'm not sure the dose that I'm talking  
8 about in terms of carrying away from the studies. If  
9 you say it should be 250 in both trials, well, if you  
10 say it should be 500, 500 was good in the first study,  
11 250 looked like 500 in the first study, it doesn't in  
12 the second study. So is it a chance fluctuation, do  
13 I really think 250 is all right, 250 is like 500, or  
14 do I think the 500 is the only thing that is sort of  
15 reproduced.

16 And I guess what I would like to hear some  
17 answers, 120 was the smaller study, the analysis was  
18 more stringent, it had a bigger placebo effect, the  
19 population was different, it was probably a more  
20 severe population.

21 Can someone from the sponsor, or the  
22 sponsor's representative help me sort out what am I

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1 supposed to carry away from the study 120?

2 DR. RYDER: Perhaps Dr. Andrews can  
3 address that. Glen? Dr. Loyd Fisher --

4 DR. FISHER: I would like to make a couple  
5 of points. To begin with, about the two studies, we  
6 had a lot of discussion about whether 120 was positive  
7 or so on. And the advice I gave the sponsor was that  
8 it was somewhat of a moot point for the following  
9 reason.

10 Let me first discuss 345. There is  
11 current guidelines out for what one large convincing  
12 study should be, and I have a paper that will be  
13 coming out in the DIA Journal in a month or so.

14 And that, at a minimum, it seems to me  
15 there have to be two elements. One is, if you weigh  
16 evidence in terms of P values, the corresponding  
17 minimum value of the two positive studies is .00125.  
18 Which study 345 makes handily.

19 The other reason, well, at least one other  
20 very good reason, we want two different studies to be  
21 positive is to show the results can be replicated in  
22 different settings, that there isn't -- otherwise

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1 there may be something very idiosyncratic.

2 And the approach that I have advocated in  
3 this article, and that we did here was, I said, if I  
4 was going to divide the clinics up, they have two  
5 separate studies, I would divide them up in ways such  
6 that the minimum power was as large as possible, which  
7 is equivalent to saying, try to make the sample sizes  
8 in your two subsets of your sites, which you are going  
9 to mentally think of as different studies, as equal as  
10 possible.

11 We did that, we only did it once, we  
12 didn't fiddle around, and in fact it wasn't even run  
13 until two days ago. But, not surprisingly, given the  
14 overall level of the P value on 345, the P values in  
15 the two parts were 0043 and 0001.

16 So I would argue that, number one, 345  
17 alone has strength of evidence equivalent to two  
18 studies, so I don't think we should really -- maybe  
19 I'm oversensitive to this, because of the recent  
20 history of this committee, and the arguments about P  
21 values around .05 and so on.

22 So I think it is somewhat of a moot point.

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1 120, if you read the protocol, I went back and got the  
2 original protocol, actually doesn't totally specify  
3 the test. They talk about 6, 9 and 12 months, but the  
4 first paragraph says that it is a six month endpoint,  
5 which I think is kind of silly, actually, in a 12  
6 month study. But be that as it may.

7 And they say they will use a log rank  
8 test, but there is at least two log rank tests you  
9 want to use in that setting, the most natural one to  
10 me would be a log rank test that takes account of the  
11 fact that this is a dose ranging study, and we at  
12 least expect a monotone response.

13 Apparently the P value they had in mind  
14 was the omnibus 3 degree of freedom log rank test for  
15 these four different parallel groups, which is not  
16 significant.

17 But if you take 6, 9 and 12 months, and  
18 you take the linear test for trend, with the log rank,  
19 and the omnibus test, out of those six tests the only  
20 one that failed, actually, was the .125.

21 So I commend them for their honesty, but  
22 mentally I told them, to me, if it is not a positive

1 study it is within Epselom, but it is a very moot  
2 point.

3 The second thing you brought up was how  
4 consistent are the results. I haven't actually looked  
5 at the confidence intervals, and so on, but my -- from  
6 having read through it, is that it is really not that  
7 inconsistent.

8 I've often made the statement, I've never  
9 seen a totally consistent clinical development  
10 program. And I think it relates to just the multiple  
11 issue. I don't see a great discrepancy between it.  
12 It looks to me like 250 works, 500 works better, but  
13 I do have to say, once I'm convinced something works,  
14 I don't take the dose so much as a hypothesis testing  
15 thing, everything has to differ at the 5 percent  
16 level. I think it is an estimation  
17 problem where you try to estimate those response.

18 DR. D'AGOSTINO: If you had 19,000  
19 subjects in your study, I guess I'm sort of  
20 sympathetic to the idea of one study. If you have a  
21 few hundred subjects I start worrying that maybe the  
22 one study isn't enough. That is an issue which we can

1 carry on here, obviously.

2 This notion of the consistency, in the  
3 writing of the protocol, if I read the protocol  
4 correctly in terms of the way it was designed and what  
5 have you, there was a lot of enthusiasm to see an  
6 effect on all these different drug doses, and the  
7 study was powered in such a way that they were  
8 basically thinking that they were going to see an  
9 effect on all the doses, and they didn't see it.

10 So I don't know if they really knew what  
11 was going on after 345, maybe they did, but maybe they  
12 didn't. The point still comes, the point comes, I  
13 guess, that I don't think you have answered my  
14 question in how do I interpret the studies, specially  
15 120.

16 What is the dose that is being  
17 recommended, what do I carry away from this, this is  
18 the dose, or how do I -- is it regiment? Listen, I'm  
19 willing to listen to a lot of different answers. Is  
20 there a sort of sequence that you go through? I'm not  
21 sure it is clear to me what it is that is being  
22 recommended.

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1 DR. LIPICKY: Well, Steve -- it is  
2 recommended, start at 500, go below the dosing  
3 algorithm where you look at the estimated creatinine  
4 clearance with Cocockroft--Gault equation, and so on.

5 DR. TEMPLE: Not 250?

6 DR. LIPICKY: I'm sorry, there were 15  
7 arms, all told, in those four trials. And the thing  
8 ordered every time, right? That is placebo was the  
9 lowest, the next highest, the lowest dose was next,  
10 the next highest dose was next, the next highest dose  
11 was next?

12 DR. D'AGOSTINO: I don't know if you can  
13 call 46 versus 51 percent --

14 DR. LIPICKY: You are looking for a  
15 statistically significant difference between the two  
16 points. I'm just saying that there were four chances  
17 to order 15 arms, and each time it turned out --

18 DR. LIPICKY: But in 120 -- no, in study  
19 120 it was 29 for the 125, it was 28 for the 250, and  
20 for the 12 months. I mean, I don't know if we should  
21 look at numbers, if --

22 DR. LIPICKY: I'm looking at three months.

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1 DR. D'AGOSTINO: So, I mean, I don't know  
2 if that is the point.

3 DR. LIPICKY: But what is the likelihood  
4 of that happening if in fact there isn't a dose  
5 related effect?

6 DR. D'AGOSTINO: What is the dose that we  
7 are carrying away, where do we start off --

8 DR. LIPICKY: No, different question. I  
9 don't -- well, I'm going to advocate something, and I  
10 will argue this a couple of times this afternoon.

11 The idea here is not to pick a dose. The  
12 idea here is to figure out whether it is, whether it  
13 works --

14 DR. D'AGOSTINO: That is an answer.

15 DR. LIPICKY: And then you have to figure  
16 out how to use it.

17 DR. D'AGOSTINO: That is an answer, and  
18 that would be an answer to my question, what do I  
19 carry away from this here in terms of how to interpret  
20 it. That is an answer.

21 DR. LIPICKY: But if you believe what I  
22 just said, and other people around the table may not,

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1 how would that influence your thinking?

2 ACTING CHAIRMAN CALIFF: Well, Ralph, I  
3 thought the sponsor had been pretty clear about their  
4 interpretation, at least, of a dosing regimen, not a  
5 dose.

6 DR. D'AGOSTINO: But how do the studies  
7 line up with --

8 DR. LIPICKY: With what they are  
9 recommending?

10 DR. D'AGOSTINO: The 120, the study 120  
11 actually laid that out. Is the 120 consistent with  
12 that? I'm not sure it is, is it?

13 ACTING CHAIRMAN CALIFF: So what you are  
14 really asking, then, I think is does -- how does 120  
15 support the conclusion that they came to about the  
16 dosing regimen that they chose?

17 DR. D'AGOSTINO: Right.

18 DR. RYDER: As far as the creatinine  
19 clearance, I just wanted to mention about the temporal  
20 sequence. Virtually, in fact, I think the entirety of  
21 345 was conducted after the amendment was introduced,  
22 and for 120 I can be corrected, but my memory is about

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1 70 percent of the patients were entered after the  
2 amendment.

3 So it is about 30 percent of the patients  
4 before the amendment. So about 30 percent of the  
5 patients, for example, would have been receiving 500  
6 micrograms BID before the amendment, even though their  
7 creatinine clearance was actually, say, 50.

8 Whereas our current recommendation, and  
9 after the amendment would be, from the get go, from  
10 day one, they would be receiving 250 in order to get  
11 their exposure in the zone that we wanted.

12 DR. D'AGOSTINO: Can I go to another  
13 question? In terms of the way the studies were, and  
14 the way the drug is laid out, if I understand it,  
15 there is this ability to convert, and then there is  
16 the ability to prolong the interval.

17 I'm not sure, again, are we saying that in  
18 the ability to convert that there is differences  
19 across the drugs, or are there not? Is there a  
20 difference between the drug and the placebo, with the  
21 500 starting, versus the placebo, is there a  
22 difference between it?

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1           Is the drug, in fact, producing more  
2 individuals converting, is that being said by the  
3 company? If I look at the numerical individually, the  
4 number of individuals here that are in these analysis,  
5 they seem to be the same.

6           So there is this bit of the -- the  
7 converting seems to have favored the drug, yet when I  
8 look at the number that in the analysis population,  
9 that all seems to have the same numbers of  
10 individuals.

11           Could you just explain how these tables  
12 sort of look different from each other? One is the  
13 significance with these Kaplan-Meier curves, and the  
14 other seems to have the same, approximately the same  
15 number of subjects in these final 12 month analysis,  
16 and six month analysis.

17           DR. RYDER: Perhaps Dr. Friedrich can  
18 review the design. The design included both  
19 pharmacological conversion, and then if you didn't,  
20 which very few people did on placebo, and about 30  
21 percent did on Dofetilide 500 micrograms, you are  
22 electrically cardioverted, then you were back in

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1 normal sinus rhythm if -- except for the 20 percent  
2 who did not get back into normal sinus rhythm, and  
3 then you were receiving blinded drug for the duration  
4 of the trial to see if that normal sinus rhythm was,  
5 in fact, maintained.

6 DR. D'AGOSTINO: Okay, good. Then as you  
7 produce individuals dropping out along the way, were  
8 those individuals not who went back to AF, but  
9 individuals who dropped out, were those individuals  
10 being considered censored individuals in the analysis,  
11 or were they being considered failures in the  
12 analysis?

13 DR. RYDER: Dr. Andrews, go ahead.

14 DR. ANDREWS: They were considered  
15 censored. But I would add a corollary to that. We  
16 actually did another analysis which actually treated  
17 them as failures, in study 345.

18 DR. D'AGOSTINO: So if you went to  
19 failures it still would have come out the same?

20 DR. ANDREWS: It still came out the same.

21 DR. D'AGOSTINO: And in terms of the  
22 hazard ratios that were done, did you use Kox

1 regression on those analysis to get the hazard ratios?

2 DR. ANDREWS: Yes.

3 DR. D'AGOSTINO: And did they carry any  
4 problem about the proportionality? I'm not  
5 questioning them so much, but did you worry that the  
6 analysis may be a bit --

7 DR. ANDREWS: We looked for evidence in  
8 non-proportionality, and there was some in the first  
9 couple of days.

10 What I would say, though, is both the log  
11 rank and the proportional hazard models basically gave  
12 the same conclusions in terms of inference.

13 DR. D'AGOSTINO: Just one last question.  
14 When I think of AF, I think of lots of people with  
15 stroke, for example, and lots of people with other  
16 serious ischemic type conditions.

17 And I know we've wandered in and out of  
18 it, but I would just like to hear the answer. What is  
19 being suggested for those individuals who are recently  
20 from stroke, and so forth, in terms of how the package  
21 is being put together?

22 DR. RYDER: Excuse me, Dr. D'Agostino, are

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1 you referring to the number of people who had a stroke  
2 in the clinical program? We can report those numbers  
3 to you.

4 DR. D'AGOSTINO: No, in terms of what --  
5 is anything being suggested in terms of how this drug  
6 is actually going to be used for those type of  
7 individuals?

8 DR. RYDER: Used in patients who had a --

9 DR. D'AGOSTINO: Who just came out of a  
10 stroke.

11 DR. RYDER: Unstable patients were  
12 precluded from admission. But if they had a history  
13 of a cerebral vascular event in the relatively distant  
14 past, then they were included.

15 DR. D'AGOSTINO: So historically they  
16 could be from stroke, but not recently from --

17 DR. RYDER: I believe that that is  
18 correct, yes.

19 DR. D'AGOSTINO: Great, thank you.

20 ACTING CHAIRMAN CALIFF: Ralph, I wanted  
21 to ask you one question, it is along the lines of  
22 interpreting the total package.

1           What we saw were a number of studies, I  
2 think something like 12, all in related rhythm  
3 disturbance problems, and then there are two which  
4 form the pivotal package.

5           And if I understood what you said, one you  
6 felt strongly met the positive trial criteria, the  
7 other at least by a binary yes or no, would not be a  
8 classical P less than .05 for a pre-specified primary  
9 endpoint.

10           How do we consider the other ten trials in  
11 terms of thinking about what the P value is? At first  
12 shot it doesn't seem quite right that you would ignore  
13 them.

14           I mean, if you did 12 trials and two were  
15 positive, to only think about the two that were  
16 positive?

17           DR. D'AGOSTINO: I think it is a good  
18 question, I'm not sure I know how to answer it in a  
19 sense of giving you a quantitative answer to it. I  
20 think that these are ways you put the data together  
21 and what have you.

22           I don't think that any of them are sort of

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1 overwhelming that you say that they make up another  
2 study, if that is the question that you are asking.

3 DR. RYDER: Dr. Califf, may I clarify one  
4 point? There were four trials in what Dr. Kowey has  
5 termed persistent atrial fib. Two dose ranging  
6 trials, 311 and 320, that were both conducted prior to  
7 the creatinine clearance amendment, and included a few  
8 patients at 750 micrograms BID.

9 They are presented in your briefing book,  
10 and the other two trials are the ones that are under  
11 discussion. The remainder of those trials were the  
12 ones that Dr. Kowey was referring to, that were in  
13 patients with paroxysmal disorders, either PAF or only  
14 PSVT that Dr. Lipicky referred to, and one was a mixed  
15 bag, both PF and PSVT.

16 So 8 paroxysmal, 4 persistent, 2 early  
17 dose ranging, and then these two.

18 DR. D'AGOSTINO: Yes. And I just don't  
19 think you can do much with those others, but look at  
20 them.

21 ACTING CHAIRMAN CALIFF: Yes. I guess --  
22 I don't want to dwell on this too much, but I think --

1 we commonly see this, and one person may look at this  
2 and say paroxysmal is clearly different than  
3 persistent, and another person might say, there is a  
4 lot in common between paroxysmal and persistent atrial  
5 fib.

6 It is perplexing that the drug would work  
7 in one and not the others, no explanation for why they  
8 should be different, and that somehow ignoring the  
9 other trials doesn't seem --

10 DR. D'AGOSTINO: Well, this is what I was  
11 trying to get at, even within this context, in terms  
12 of the regiments and so forth. It isn't clear, from  
13 the two trials, that even the regimen that worked in  
14 one works in the other, is it a smaller sample, is it  
15 a more sever population, is it a placebo effect that  
16 is larger?

17 It would have been nice to have a  
18 discussion that would have said let's take a look at  
19 the numbers and see what we can make out of what this  
20 study shows, as opposed to suggesting that one study  
21 is enough.

22 ACTING CHAIRMAN CALIFF: Bob?

1 DR. TEMPLE: Ralph, I thought Rob was  
2 raising another question that has never been raised at  
3 any of these sessions, but I want to raise it, because  
4 we slightly raised it in a document we wrote.

5 He is basically saying, suppose you did  
6 ten studies of a variety of things, total mixture of  
7 things. And it is in an exploratory mode, you don't  
8 necessarily expect it to work in all those, but nine  
9 of them show nothing, so you throw those away, you  
10 don't bother us with them. One of them works out.

11 What is the true P value? Let's say there  
12 is only one in chronic atrial fibrillation. Now, do  
13 you get to just say, okay I only have one trial, I  
14 don't have to make any adjustment, or do you have to  
15 sort of count the environment out of which these thing  
16 arose?

17 And I want to say, no one has addressed  
18 that point, to my knowledge, anywhere, and it is  
19 terrifying.

20 When I first raised that point with Dr.  
21 Woodcock, she said, yes we also have to consider all  
22 the trials done in the parallel universe, too. An

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1       ironic statement to point out that this is a very  
2       hairy kind of problem.

3               But it is one of the main reasons that you  
4       want replication, because if one of them is just a  
5       fluke, you really don't expect to see the same thing  
6       in the next one, in the very same place.

7               So I thought that is what Rob was sort of  
8       starting to get at, and it is a very interesting  
9       question.

10              DR. D'AGOSTINO: Yes, that is the way I  
11       tried to answer it, as opposed to the particulars, is  
12       that what do you do with the accumulation. I think in  
13       this case here, that there isn't much information that  
14       you can get out of it, but I think in general there  
15       may be some good information.

16              Even though a statistician, I get very  
17       concerned when people start attaching P values to  
18       these things in a retrospective fashion, and I would  
19       like to sort of suggest that one carries away, to  
20       start with, that does it supply some information and  
21       justification for it as opposed to attach  
22       automatically a P value.

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1 DR. TEMPLE: I have one other question for  
2 you, though. The -- I understand your reservations  
3 about the 120, because it didn't exactly line up with  
4 all the pre-specified end points. But you also seem  
5 to be saying that it suggested something different  
6 about dose.

7 And I must say I don't see that. They  
8 seem to order the same way, even if they are not, even  
9 if the comparisons don't show up. And, you know, the  
10 higher dose is always considerably better than the  
11 other one, or at least it looks that way.

12 DR. D'AGOSTINO: And that is an answer  
13 also. I mean, what I wanted to hear is what the  
14 sponsor had to say about it, because the 250, in the  
15 study 120, the 250 dose looks very much like the 125  
16 dose, so is there something that you just don't -- I'm  
17 using the book that the FDA put together, which I --

18 DR. TEMPLE: That is true, but 500 looks  
19 different from both of them in both.

20 DR. D'AGOSTINO: Exactly, and that would  
21 have been an explanation, that we are focusing on the  
22 500, but then what happens to the 250? I mean, is it

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1 something that is a population that you need to use a  
2 higher dose, and then are we getting in a situation  
3 where you need something like 500 and suddenly it is  
4 creeping up to 700 in natural practice, where we are  
5 a bit concerned.

6 So that is the type of question I was  
7 asking.

8 DR. RYDER: Dr. Califf, Dr. Friedrich  
9 thinks he may have a point about --

10 DR. FRIEDRICH: Can I make one point that  
11 might just answer your question? Because I think  
12 there is a little bit of a confusion here.

13 In study 345 the primary endpoint looked  
14 at an analysis which took the maintenance population,  
15 as we call it, which are all patients that made it  
16 into sinus rhythm, okay?

17 So if we look at slide 13, that is a  
18 maintenance population. And if you compare this to  
19 study 120, where the maintenance population was the  
20 secondary endpoint, I would submit to you that you see  
21 very similar things.

22 So can we have efficacy core slide 13,

1 please? At the one year.

2 So, in other words, here you see the dose  
3 response relationship that was mentioned by Dr.  
4 Temple. When you go up one dose level you see more  
5 efficacy starting with 125, 250, and 500.

6 Now, can I have slide 20, please? And  
7 then here is the same analysis, starting again with  
8 all those patients that made it into sinus rhythm.  
9 And, again, you see less of a difference between 125,  
10 and 250, but you still see, you know, up to 500.

11 DR. D'AGOSTINO: I don't want to beat this  
12 over and over again. In study 120 the 250 dose is  
13 very close to the 125; in study 345 the 250 dose is  
14 very close to the 500, and that is the point I was  
15 trying to make, or making, and what you said doesn't  
16 contradict that.

17 DR. LINDENFELD: Just one point. In the  
18 two studies wasn't there a difference when there was  
19 a dose reduction in how they were given? I think 345  
20 was -- the dose reduction was given only once a day,  
21 and in 120 the dose was reduced, but given twice a  
22 day.

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1           And that may have a little bit of bearing  
2           on efficacy, or the difference in the doses.

3           DR. FRIEDRICH: You are quite correct that  
4           you are stating that in 345 some patients received,  
5           some patients that were dose adjusted received a once  
6           a day dose regiment. That is correct.

7           DR. LINDENFELD: Like I said, this is what  
8           has to come up again if we decide we want to -- how we  
9           are going to dose it, if the dose is reduced, that is  
10          going to be an important question.

11          DR. D'AGOSTINO: That is what I'm trying  
12          to get out of the discussion.

13          DR. FRIEDRICH: We felt justified to do  
14          that because the AUCs between regiment of 250 BID and  
15          500 QD were very similar. And, in fact, when you look  
16          at the outcome of those patients dosed with 500 QT in  
17          study 345, also those in 120, dose 250 BID, you see a  
18          similar hazard ratio.

19          If you are interested I will look for the  
20          slide.

21          DR. RYDER: These are patients with the  
22          creatinine clearance below 60. He is talking about

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1 lower creatinine clearances.

2 DR. FRIEDRICH: Backup slide 99, yes.

3 DR. RYDER: If I could make one comment  
4 while those slides are coming up, I just got data from  
5 Glen. If you look at 120 and 345, the confidence  
6 intervals overlap between the two studies for every  
7 dose for maintenance.

8 So it is consistent with statistical  
9 variability. That doesn't show it is there, but --

10 DR. D'AGOSTINO: But it is only the 500  
11 that beats out the placebo, and the 120 -- so you may  
12 have just said a statement that everything is equal,  
13 even 500 is equal to the placebo, because 500 is equal  
14 to 250, 250 is equal to 125, 125 is equal to the  
15 placebo.

16 So I'm looking for a simpler answer, I  
17 guess.

18 ACTING CHAIRMAN CALIFF: Dr. Atkinson, you  
19 had a point, then I want to go around to everyone  
20 else, and if we could try to avoid discussing things  
21 we've already discussed.

22 DR. ATKINSON: Thank you, Rob. I would

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1 like to try to bring two discussions that we've been  
2 having together, and maybe we could have core efficacy  
3 slide number 24, please.

4 We've been discussing the fact that it is  
5 not surprising, if you lower the dose, according to  
6 the dosing algorithm, you can reduce the incidence of  
7 Torsade.

8 But we've been talking about efficacy,  
9 we've been talking about fixed doses. And I think it  
10 is important for us to consider, since we are being  
11 asked by the sponsor here not to approve a fixed dose,  
12 but a dosing algorithm to think a little bit about  
13 what does the dosing algorithm do to efficacy.

14 And this slide troubles me a little bit  
15 because it seems to me that, first of all, there is a  
16 very small N involved. But it looks to me, on the  
17 bottom here, that when you reduce the dose according  
18 to your algorithm, that the confidence interval for  
19 efficacy and maintenance therapy now overlaps the null  
20 point.

21 I wonder if the sponsor would like to  
22 comment on that?

1 DR. FRIEDRICH: You are correct that the  
2 confidence interval overlaps, and it is probably an  
3 effect of the small numbers that you see here. But on  
4 average efficacy is preserved in these patients.

5 DR. ATKINSON: But these are your two  
6 pivotal studies, is that right? And you are asking us  
7 to approve not a fixed dose of say 500, but a dosing  
8 algorithm where a dose is adjusted according to  
9 creatinine clearance?

10 DR. RYDER: And this is a segment, this is  
11 segmenting the entire randomized group. Thirteen more  
12 patients are actually included, and Till doesn't have  
13 them on the slide here because our statisticians  
14 wouldn't allow us to put them on the slide, because we  
15 could not have -- did not have a comparable placebo  
16 group that had dose adjustment for QTc prolongation.

17 And that was where he said nine out of  
18 those thirteen patients had maintenance of sinus  
19 rhythm at twelve months.

20 So I guess that is a point estimate of  
21 like .75, or something. But we weren't allowed to do  
22 that. I would just point out that those 13 plus these

1 41 is 54 plus the 106, that is the entire group that  
2 was randomized, and this is sort of segmenting it  
3 down, and what you see are the data in the confidence  
4 limits.

5 DR. ATKINSON: My concern here is one that  
6 Bob Temple referred to earlier, and that is that we  
7 may not be able to separate efficacy from toxicity  
8 here. And also in the spirit of one of Dr. Temple's  
9 admonitions to us to think a little bit out of the  
10 box, if you could show core slide 35?

11 It shows what happens when patients are  
12 started on therapy, and I believe this is without a  
13 loading dose that we are looking at the institution of  
14 various maintenance dose programs.

15 The -- this is sort of an inverse Kaplan-  
16 Meier type curve showing response of patients with  
17 time. And if you look at the top curve, when it does  
18 appear, you will see that most patients are converting  
19 within about 36 hours, which is not unreasonable, if  
20 you can sort of visualize the blood levels increasing  
21 over time to reach a steady state, and let's say 90  
22 percent at steady state, and 3.3 half-life, so that is

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1 -- if it is a ten hour half life, this response curve  
2 is roughly mirroring what the blood level probably is  
3 doing.

4 The point is, there are some patients who  
5 are converting before 36 hours, and they are  
6 converting before they get to steady state levels at  
7 500 milligrams BID, or micrograms BID.

8 The question arises then, can the  
9 therapeutic index of this drug in clinical practice be  
10 increased by maintaining these patients at lower  
11 doses, lower effective blood levels?

12 Are these patients who are going to be  
13 more responsive to your drug than others? In other  
14 words, I think in -- as we think about dose ranging,  
15 and developing drugs we are tending to move away more  
16 and more from a maximum tolerated dose strategy to a  
17 maximally effective dose.

18 What I'm talking about here is perhaps  
19 going one step beyond your algorithm and  
20 individualizing dosage according to patient response  
21 during this -- while therapy is being started.

22 Do you have any data that suggests that if

1 a patient converts to the lower blood level, that they  
2 can be maintained effectively at a lower blood level  
3 as well?

4 DR. RYDER: That experiment was not done,  
5 the adjustment was based on their pharmacodynamic  
6 response as assessed by QTc, and downward adjusted if  
7 they had a prolongation that was excessive.

8 DR. ATKINSON: I understand it wasn't  
9 done. What I'm trying to suggest is a way that you  
10 might think of increasing the therapeutic index.

11 DR. RYDER: Dr. Friedrich, did you have a  
12 comment?

13 DR. FRIEDRICH: Yes, can I make one point  
14 on the previous slide 24, if you could bring that up  
15 again, please?

16 I think I made the point, during my talk,  
17 and I apologize if it didn't really come through; but  
18 I think you cannot exclude here the possibility that  
19 in the group reduced for creatinine clearance you have  
20 different patient characteristics. These probably are  
21 much sicker patients, the probably not just have  
22 impaired renal function, but they probably also have

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1 more structural heart disease, concomitant diseases.

2 So the comparison is not as strict, I  
3 think, looking to the statisticians here.

4 DR. ATKINSON: So you are proposing that  
5 impaired renal function is an independent factor than,  
6 for lack of efficacy of your drug?

7 ACTING CHAIRMAN CALIFF: Well, or that it  
8 goes with a constellation of other clinical findings.

9 DR. PRATT: I think in general we all  
10 appreciate the fact that patients with most severe  
11 structural heart disease keeping them in sinus rhythm  
12 with atrial fibrillation is more difficult than  
13 someone with none.

14 So that was not the only factor that was  
15 making those two point estimates different.

16 DR. ATKINSON: I understand, thank you.

17 ACTING CHAIRMAN CALIFF: Okay, Dr.  
18 Lindenfeld?

19 DR. LINDENFELD: Just a few questions.  
20 Can you reassure me that the risk of stroke is the  
21 same in the atrial fib populations between placebo and  
22 drug? Just a simple yes or no is enough.

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1 DR. PRATT: Yes, I have the numbers, in  
2 general SVA trials the risk of stroke was about one  
3 percent in both populations, the risk of stroke plus  
4 TIA and embolism in Diamond was somewhere between 5  
5 and 6 percent, both placebo and Dofetilide randomized  
6 patients.

7 DR. LINDENFELD: And can you tell me,  
8 throughout the course, at least of the atrial  
9 fibrillation studies, an EKG was done about every  
10 month. How many patients were withdrawn from  
11 Dofetilide because of a prolonged QT interval during  
12 that period of time?

13 DR. RYDER: Dr. Friedrich has that  
14 information.

15 DR. FRIEDRICH: Yes, there were 12  
16 patients. Let me get this slide up for you. It is  
17 the lower line there, CQT, QTc prolongation beyond 500  
18 or 550 milliseconds, 12 patients.

19 DR. LINDENFELD: Then how often are you  
20 going to recommend that EKGs be done in the first  
21 year?

22 DR. FRIEDRICH: Say again?

1 DR. LINDENFELD: How often will you  
2 recommend EKGs be done in the first year?

3 DR. FRIEDRICH: They were done in the  
4 clinical trials whenever a visit occurred.

5 DR. LINDENFELD: Because they were done in  
6 this trial every month?

7 DR. FRIEDRICH: Yes.

8 DR. LINDENFELD: And is that true of  
9 Diamond too, were they done every month?

10 DR. FRIEDRICH: Excuse me, did you say one  
11 month?

12 DR. RYDER: Every three months.

13 DR. FRIEDRICH: They were done every three  
14 months, I'm sorry.

15 DR. LINDENFELD: Okay, all right.

16 DR. TEMPLE: Dr. Lindenfeld, didn't you  
17 ask him to say how often they were going to recommend  
18 doing it and labeling?

19 DR. LINDENFELD: Right.

20 DR. TEMPLE: Did you hear --

21 DR. LINDENFELD: No, I didn't hear the  
22 answer yet.

1 DR. RYDER: We would be driven, I mean,  
2 the labeling discussions really haven't started or  
3 have just been -- the dialogue has just started, and  
4 information from the clinical trials is really what  
5 will drive the labeling, and as was reported we can  
6 say that --

7 DR. TEMPLE: I guess the question might  
8 have been a hint.

9 DR. RYDER: Every three months.

10 DR. LIPICKY: I thought we had to approve  
11 it before we talked about labeling.

12 DR. LINDENFELD: And what was the average  
13 ventricular response in the atrial fibrillation  
14 groups? Just the average rate, at the beginning of  
15 the protocol.

16 DR. RYDER: Baseline heart rates?

17 DR. LINDENFELD: Baseline heart rates.  
18 And as a follow up to that, maybe the same data is --  
19 how are the rate controlling drugs handled in that run  
20 in period, were they generally discontinued, or were  
21 they continued?

22 DR. FRIEDRICH: Slide 18 shows the

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1 distribution of the heart rate at baseline. And since  
2 all patients started the trial in atrial fibrillation,  
3 this is in atrial fibrillation.

4 DR. LINDENFELD: And did we see analysis  
5 of the risk of prolonged QT with the heart rate, did  
6 I miss that? Just with the baseline heart rate?

7 DR. FRIEDRICH: Yes, this was --

8 DR. LINDENFELD: Okay, I'm sorry, you  
9 showed that.

10 And did you say how the drugs, the rate  
11 controlled drugs were handled, was there any specified  
12 protocol?

13 DR. FRIEDRICH: No, there was no specified  
14 protocol that could be --

15 DR. LINDENFELD: So that was left up to  
16 the physician?

17 DR. FRIEDRICH: -- local practice, yes.

18 DR. LINDENFELD: And just my last  
19 question, in the Sotalol arm was the Sotalol dose  
20 decreased in the same way that the Dofetilide dose was  
21 decreased for QT

22 DR. FRIEDRICH: Yes, it was a double dummy

1 technique, so it was a blinded study supplied to all  
2 patients.

3 DR. GRABOYS: Was the mean heart rate, was  
4 that -- did that include individuals who were entered  
5 and they were on drugs, right? So you had -- what  
6 percentage were on Dig, for example? I mean, that has  
7 reference to ultimately discussion of quality of life,  
8 and symptoms, because if the patients are coming in  
9 with heart rates of 90 or 95, essentially no -- that  
10 is at rest, their rate control is poor, and they are  
11 going to be quite symptomatic, then.

12 DR. FRIEDRICH: Can I go to backup slide  
13 18, please? I meant to say core slide 18, I'm sorry.

14 DR. LIPICKY: Are these resting heart  
15 rates, or just any old heart rate?

16 DR. FRIEDRICH: That is resting. Here is  
17 the breakdown of concomitant medications, 80 percent  
18 on Digoxin.

19 DR. RYDER: And study 345 was similar?

20 DR. FRIEDRICH: Yes, a little bit less.

21 ACTING CHAIRMAN CALIFF: Tom, don't you  
22 think those rates are pretty representative of what

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1 you see in a population of typical patients? I mean,  
2 we would all like to think that we keep better control  
3 than that, but it looks like what we see.

4 DR. GRABOYS: Well, if those are the  
5 rates, and they were on those drugs, it meant that  
6 there was no rate control at rest, and if there is no  
7 rate control at rest, obviously not going to have any  
8 rate control when they are walking around, and they  
9 are going to be very symptomatic.

10 I mean, my point is that -- is that atrial  
11 fibrillation can be viewed as a rhythm of choice, you  
12 kind of declare victory when you are going back and  
13 forth on all these different drugs, in order to do  
14 that, then you have to be committed to significant  
15 rate control, which means the resting ECGs should have  
16 a ventricular response to AF of 50 to 60.

17 That way you can assure yourself, when  
18 they get up and walk around, they are not going to be  
19 symptomatic.

20 ACTING CHAIRMAN CALIFF: But you would  
21 also agree that that strategy has never been tested?

22 DR. GRABOYS: Good point.

1           ACTING CHAIRMAN CALIFF:    It is your  
2 preferred strategy, but it has never been tested in a  
3 clinical trial?

4           DR. GRABOYS: We are willing to accept all  
5 comers.

6           DR. TEMPLE: What sort of dose of Dig were  
7 they on, for one thing, and would you, in your  
8 clinical estimation, you ordinarily need to achieve  
9 reasonable rate control? I mean, Dig for heart  
10 failure has come down, and we all hope that mortality  
11 is coming down with it.

12           What is the dose you need here for rate  
13 control?

14           ACTING CHAIRMAN CALIFF: I think that is  
15 a point of great confusion. I would be delighted to  
16 hear a clear answer from one of our electrophysiologic  
17 colleagues.

18           DR. KOWEY: I don't think this works at  
19 any dose, very well. And people with normal AV nodes,  
20 I think the only time we see Dig work in patients with  
21 AF is in patients that have conduction system disease.

22           DR. GRABOYS: I mean, that raises a whole

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1 other issue, which we haven't even talked about, is  
2 the age issue. I have no idea whether you are looking  
3 at 85 year olds who are AF, or 80 year olds in terms  
4 of their problems, or their issues.

5 If you are 80 years old, and we are trying  
6 to rate control, Dig can be very helpful, because they  
7 have intrinsic increased phagiatonia and they may have  
8 some conduction abnormality to help with rate control.

9 I agree with you, Peter, that 65 year old  
10 who comes in on the traditional doses of Dig, is not  
11 going to have great rate control, unless you use it in  
12 concert with a calcium channel drug you are using, in  
13 concert with a beta blocker.

14 DR. RYDER: Dr. Graboys, would you like to  
15 see the age distribution of the patients?

16 DR. GRABOYS: Sure.

17 ACTING CHAIRMAN CALIFF: I think you have  
18 shown that a couple of times already. And they were  
19 an old population.

20 DR. FRIEDRICH: In 345 the breakdown of  
21 the population age.

22 DR. TEMPLE: So what sort of doses would

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1 people be getting for the lack of effect that Peter  
2 thinks is there, or the effect that people think is  
3 there?

4 DR. RYDER: Do we have information on the  
5 dose of Dig? I'm not sure we have that right now, but  
6 we can ask some of the technical people to try to  
7 search for it.

8 DR. LIPICKY: I don't know the single  
9 trial that has looked at that.

10 ACTING CHAIRMAN CALIFF: We are all in a  
11 great state of confusion right now because the Dig  
12 trial, as you know, seemed to indicate that patients  
13 on a lower dose of Dig had a better survival.

14 And, of course, that is not a population  
15 with atrial fibrillation, but it makes one worry about  
16 the higher doses that used to be advocated, where we  
17 said, don't worry about the Dig level, just give a  
18 dose until you control the rate.

19 So I don't think that there is going to be  
20 much useful discussion about what the right dose of  
21 Dig is, because there is no --

22 DR. TEMPLE: I wasn't asking what the --

1                   ACTING CHAIRMAN CALIFF:  -- it is just  
2                   opinions.

3                   DR. TEMPLE:  -- I just wanted to know what  
4                   the actual dose usually is, and would then worry  
5                   appropriately depending on how high it is.

6                   ACTING CHAIRMAN CALIFF:  Tom Bigger is  
7                   probably -- you've looked at this as much as anybody.  
8                   What are people using now?

9                   DR. BIGGER:  Using much -- they tend to  
10                  add a beta blocker instead of pushing the DIG.

11                  ACTING CHAIRMAN CALIFF:  Okay --

12                  DR. LINDENFELD:  Can I?

13                  ACTING CHAIRMAN CALIFF:  Yes.

14                  DR. LINDENFELD:  Just one final question,  
15                  I just wanted to hear a little speculation.  We saw  
16                  the risks with many type III drugs for Torsade,  
17                  prolonged QT interval, structural heart disease,  
18                  female gender, and yet none of those were significant  
19                  with Dofetilide.  And yet it is a very clear type III  
20                  drug.

21                  Could I just hear why?  I mean,  
22                  speculation?

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1 DR. RYDER: Speculation why the mortality  
2 is --

3 DR. LINDENFELD: Why we don't see those in  
4 your analysis as a risk for Torsade with Dofetilide?  
5 And that is true with all the other type III drugs.

6 DR. PRATT: Just to reiterate the data  
7 base that we presented today, like all IKR blockers,  
8 there is definitely a risk of being female and taking  
9 Dofetilide for the risk of Torsade de points  
10 ventricular tachycardia.

11 With this specific treatment algorithm an  
12 inpatient initiation and adjustment of dose, there is  
13 no mortality signal. And I think that is the  
14 difference.

15 ACTING CHAIRMAN CALIFF: Dr. Piña?

16 DR. PIÑA: I want to follow up on Joan's  
17 point about the EKG frequency. Since some of these  
18 patients seem to have had very little symptoms to  
19 start with, they could have reverted back to atrial  
20 fibrillation before the three months. And if you  
21 haven't done the EKG, you may not know it.

22 I mean, a lot of my patients don't even

1 realize when they go back into atrial fib. So maybe  
2 the three month frequency isn't that great in people  
3 who recur, they usually recur pretty quickly. And  
4 that was one of my observations.

5 I have a question, are you going to have  
6 an assay for blood levels of this drug made available?

7 DR. RYDER: Dr. Pratt, do you want to  
8 address the utility, or Don Nichols? I mean, perhaps  
9 I can take it.

10 The short answer is that we believe that  
11 by assessing QTc you are looking at one step better,  
12 you are looking at pharmacodynamic responsivity, and  
13 a very nice correlation between QTc and plasma level  
14 has been shown.

15 And so we are going one step better. We  
16 are assessing not just the individual plasma level,  
17 but the response of that person, that individual to a  
18 certain plasma level.

19 And if they are one of the people who  
20 respond with a higher QTc, we are suggesting that they  
21 down-titrate after the first dose, or if it persists,  
22 at the level of 500 milliseconds, that the be

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1 discontinued, that they be dropped from the  
2 Dofetilide.

3 DR. PIÑA: And I have just one final  
4 observation, the comparison between CHF stat and the  
5 Diamond CHF trial, I don't believe that the mortality  
6 is the same. I think that the mortality in the Diamond  
7 CHF at six months is higher than the CHF stat trial.

8 So I'm not sure that comparison is valid.

9 DR. RUSKIN: Yes, it is true that the  
10 mortality rate is somewhat higher in Diamond CHF than  
11 in CHF stat. I think the key point is that there was  
12 absolutely no difference between treatment groups in  
13 the two trials.

14 But you are right, there is a higher  
15 absolute mortality rate in the Diamond CHF than in the  
16 Amiodarone trial.

17 DR. PIÑA: And most of your population was  
18 really class 3, you had a few class 4's but it was  
19 primarily class 3, and that to me looks like a little  
20 high mortality for six months in class 3. I don't  
21 know what Dr. Konstam thinks of that, the six month  
22 mortality in Diamond CHF.

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1           ACTING CHAIRMAN CALIFF: I might comment  
2 on that, because we are interacting with the Diamond  
3 investigators now in other trials, and it is a unique  
4 system in Denmark, where they actually enroll sick  
5 patients in trials as a matter of policy, and at least  
6 their argument, in the number of trials they've done  
7 is that in the U.S. we tend to exclude anyone who  
8 would be at risk of dying, people that we are worried  
9 about.

10           They consistently see a higher mortality  
11 and maintenance because they actually enroll most  
12 patients. So it is not unique to this particular  
13 comparison, but in other trials that they do.

14           Now, we could talk a long time about  
15 whether we believe that is a correct argument, but  
16 that is at least what they've said.

17           Tom, do you have issues?

18           DR. BIGGER: I just have one issue. I  
19 wondered how you were going to approach it? And,  
20 again, this may just come up in the negotiations. But  
21 starting on this premise, that the fundamental action,  
22 electrophysiologic action of Dofetilide that relates

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1 to its efficacy, is also related to the increase in  
2 QT, and the Torsade de points risk.

3 And there is not, there is overlap in the  
4 concentrations that produce efficacy and prolong the  
5 QT, that drug interactions may be critically important  
6 here.

7 And a number of drugs that even your own  
8 spokesman said thought would bear some further study,  
9 have yet to be done, which I guess translates into  
10 very conservative labeling, or further studies, or  
11 both, to make doctors comfortable in prescribing this.

12 Because I think doctors hearing what we  
13 are hearing, are likely to dose lower than what you  
14 recommend because they are nervous, although people  
15 over here seem to think they are going to be  
16 overdosing folks.

17 And I just wonder, what is your approach  
18 going to be to this drug interaction problem in terms  
19 of labeling, or further studies, or how are you going  
20 to approach that?

21 DR. RYDER: I think it was summarized by  
22 Dr. Pratt, and I completely agree with what he said.

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1 As far as labeling goes, I think the information that  
2 we have should be presented as we gather new  
3 information.

4 And he mentioned a number of clinical  
5 trials, clinical pharmacology trials that he has  
6 recommended to us, and he is our expert consultant in  
7 this area, and we are going to be discussing with him,  
8 and with the Agency, and be working from that place  
9 forward.

10 As more information comes in, I would  
11 think that the labeling would evolve.

12 DR. KOWEY: I just want to follow up on  
13 that, because I'm still stuck on this Dig question.  
14 And I know, Craig, when you presented the data, and  
15 when you were making your presentation, as we had  
16 requested you to do, you focused on the mortality, but  
17 you didn't talk about the Torsade.

18 And I agree with you that we all want to  
19 know about mortality, but I'm also worried about  
20 Torsade. And this questions that Tom just asked, the  
21 reason it made me think about it is because it is  
22 going to come down to a labeling question.

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1           What are we going to tell doctors about  
2 using this drug with Digoxin? Do you think that that  
3 finding of more Torsade with Digoxin is real, or not?

4           DR. PRATT: Well, why don't we go back to  
5 the data? It is a good place to go, I guess. Let's  
6 start with backup 20.

7           And this, of course, is all in that drug  
8 interaction document, Peter, and you are well aware of  
9 it. So it had already been discussed, and so this is  
10 the information unadjusted and adjusted.

11           Of course, people on Dig are different  
12 than people not on Dig. And this is a five thousand  
13 and fifty some patient data base of which about 2,400  
14 are on Dig, so it is pretty robust, so there is a lot  
15 of deaths. So 1,115 deaths.

16           So the risk ratio there of adjusted is 2.  
17 And there -- as you know, statistical adjustment is  
18 not exactly the same as taking into consideration  
19 everything that is different about those patients.

20           And then if we go to the next slide, those  
21 are the point estimates of mortality, and the  
22 confidence intervals around that point estimate for

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1 Dig, given that there are 2,300 patients is fairly  
2 narrow.

3 Now, what are the limitations of the data  
4 base? Well, there is only, thank goodness, 43 cases  
5 of Torsade. There is 1,016 deaths. Statisticians  
6 would have to tell you and I, Peter, how much we can  
7 really make out of that when we go to section this up  
8 and slice it, and dice it in 15 ways.

9 So that is the information. I certainly  
10 think that right now there is no compelling data to  
11 say that you can't use Dig to control rate in atrial  
12 fibrillation.

13 However, it is not my drug of choice,  
14 anyway.

15 DR. RYDER: Dr. Califf, I just want to  
16 point out, and it is in your briefing document, I'm  
17 sure that you've reviewed it. But the information  
18 comes from the combined Diamond plus SVA data set.

19 And I just think it is germane to say that  
20 there were 43 Torsade in the total 2857 patients, one  
21 and a half percent if you considered everybody.

22 If you subsetted it down to the 30

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1 patients who had Torsade on Dig, that is 30 out of  
2 355, 2.21 percent. The flip side of that I would have  
3 to do some quick math, but it would probably be in the  
4 order of, say, 0.8, or something like that, 0.9  
5 percent.

6 So I still think that it is pertinent to  
7 know that the frequency of patients taking Dig was  
8 quite high, throughout the Diamond trials. That is  
9 the bulk of the information that we are providing the  
10 committee in terms of the safety of Dofetilide, and  
11 specially its mortality signal that Dr. Pratt is  
12 referring to.

13 DR. PRATT: Peter, just one last point.  
14 I mean, there are three deaths in patients  
15 attributable to Torsade. Once you get to be an  
16 outpatient the only signal we can look for Torsade is  
17 arrhythmic death, syncope, total mortality. We've  
18 looked at all those in every possible way.

19 ACTING CHAIRMAN CALIFF: Marvin?

20 DR. KONSTAM: Craig, let me -- I have a  
21 couple of questions, but this sort of leads into one  
22 of them, so let me ask it now.

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1                   You know, we have -- you have 12 deaths in  
2 the supraventricular arrhythmia data set on Dofetilide.  
3 And can we -- can you tell us anything about those  
4 deaths?

5                   And I guess the question there, in follow-  
6 up to the point that you just made, is how are we  
7 going to be assured that those are not related to  
8 Torsade?

9                   DR. PRATT: Well, of course you are not  
10 going to be sure, because outpatient deaths, our  
11 classification system kind of stinks, as you know.  
12 And we have written some papers about that.

13                   So that is a tough thing. You can look at  
14 signals, we looked at arrhythmic death in the SVA, and  
15 it is something like 0.4 versus 0.5 percent.

16                   Actually Jeremy and I looked at the  
17 individual deaths for the presence or absence of  
18 structural heart disease. All but two of them, we  
19 think, are in patients with structural heart disease.

20                   You can look at the syncope, syncope is  
21 almost identical in peoples both in the SVA and in  
22 Diamond.

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1           So when we look at all the sort of  
2 imperfect options that we have, they all come out a  
3 wash. I've already showed you the arrhythmic deaths  
4 survival curves, Kaplan-Meier for Diamond and I've  
5 already given you the rates of arrhythmic death in the  
6 SVA population. Those are the markers that we have.

7           DR. KONSTAM: I guess the specific  
8 question that I was interested in, from anybody in the  
9 sponsor is, what can you tell us, specifically, about  
10 those 12 deaths, in terms of mode of death, or  
11 anything that helps us out in terms of what might be  
12 happening there?

13           DR. PRATT: You want to call -- whose  
14 backup is this? Safety, this is additional safety  
15 backup, probably isn't even available, is it? Just  
16 read it, I think you should read it, I can't read  
17 that.

18           DR. RUSKIN: Dr. Pratt is being supplied  
19 the information.

20           DR. PRATT: I was given a one font copy.

21           DR. RYDER: It is a simple listing of the  
22 deaths, I believe.



1 DR. PRATT: I would almost just be happy  
2 if you would take this, what specifically would you  
3 like to know?

4 DR. KONSTAM: I don't know, just what do  
5 we know about them, what --

6 ACTING CHAIRMAN CALIFF: Marvin, do you  
7 ever find mode of death analysis to be useful for  
8 anything?

9 DR. KONSTAM: Well, I tell you -- let me  
10 just say, in general terms, I -- you know, I think  
11 most of -- you know, we have an enormous data set, I  
12 think, relative to other existing approved  
13 antiarrhythmic agents.

14 And it is, in fact, going to be the source  
15 of some degree of reassurance about --

16 DR. PRATT: I just want to see you for a  
17 change.

18 DR. KONSTAM: Yes, that is good. About  
19 safety. And you've made that point a few times, that  
20 maybe we shouldn't worry too much about Torsade,  
21 because don't have a mortality signal.

22 But I think the assurance about that is

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1 coming predominantly from the Diamond trials. And the  
2 frequency of mortality, and the mode of mortality, and  
3 the drivers of mortality in those data sets, that is  
4 heart failure and post-MI, is going to be very  
5 different, all going to be very different from the  
6 superventricular arrhythmia population at large.

7 So I guess I'm still trying to look for  
8 any help I can within the superventricular arrhythmia  
9 group.

10 DR. PRATT: Let me just go through. There  
11 are three presumed placebo arrhythmic deaths, and  
12 there are -- let me see now, I have to do this fast.  
13 I think there are six Dofetilide associated presumed  
14 arrhythmic deaths, and there is almost a two to one  
15 randomization.

16 And that is how you get with that  
17 numerator denominator to 0.4 versus 0.3 percent. Let  
18 me also -- let me just tell you, the one other  
19 population I guess we would all agree is relevant is  
20 Diamond AF, in which the number of arrhythmic deaths  
21 on placebo is two higher than on Dofetilide.

22 So I mean, every data base we have --

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1 DR. KONSTAM: I hear you, and I guess we  
2 are not going to be able to draw any kind of  
3 conclusions from that. I guess I just reflect that I  
4 don't easily go from saying, we do have Torsade, but  
5 we don't have any mortality signal associated with  
6 Torsade, because that is really being driven from  
7 Diamond.

8 And I still -- we still don't know about  
9 these 12 that died, and whether some of them didn't  
10 die of Torsade. And I guess that is just -- I just  
11 reflect on it.

12 DR. PRATT: And I think it is a very valid  
13 point, and I know I don't know that either. But just  
14 let me give you a little bit of background, having  
15 been on the Sword trial.

16 I was trying to figure out what was really  
17 different about Sword and Diamond, and I think this  
18 three day initiation as an inpatient, and not just  
19 removing patients from the drug that have had Torsade,  
20 but removing patients from the drug that have an  
21 unusual QT response.

22 I think that really makes the difference.

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1 I think you remove hundreds of patients that otherwise  
2 would be at risk for this as an outpatient. And I  
3 think that is why we don't see a mortality signal.

4 DR. BIGGER: Okay. Now, I just want to  
5 ask a couple of things about the Diamond population,  
6 particularly the AF Diamond population.

7 And, again, this is in light of saying,  
8 this is the population that we are really going to try  
9 to draw some comfort from with regard to overall  
10 mortality signal.

11 So then I'm still struggling with the fact  
12 that the AF population within the Diamond trials,  
13 which is of course going to be the indication here,  
14 AF, was managed differently, somewhat differently by  
15 somewhat different algorithm than we are thinking is  
16 going to be the treatment algorithm, namely that they  
17 started on a lower dose, regardless of -- even with  
18 the normal creatinine clearance.

19 So I guess I will start, first question I  
20 have about that is, why did you do that, why did you  
21 decide to, you know, to start all of the Diamond AF  
22 patients on a lower Dofetilide dose?

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1 DR. RYDER: Dr. Marshant?

2 DR. MARSHANT: This is something that was  
3 recommended, or in fact, insisted upon by the Diamond  
4 steering committee at the initiation of the study, and  
5 their concern was, as explained earlier, was that in  
6 these patients who were particularly sick with very  
7 severe structural heart disease that the risk of  
8 proarrythmia may be that much higher.

9 DR. KONSTAM: No, but it is the group with  
10 structural heart disease who have AF that you started  
11 on the lower dose?

12 DR. MARSHANT: There was concern within  
13 the steering committee that short long short sequence  
14 that would be typically seen in atrial fibrillation  
15 patients may predispose to Torsade.

16 DR. KONSTAM: So I guess the question,  
17 then, that follows from that is how do we know you  
18 weren't right? I mean, how do I know that -- I mean,  
19 that was your reasoning going in, that this AF  
20 population was going to be more subject to Torsade,  
21 and presumably mortality, than the overall Diamond  
22 population.

1                   And so you manage them differently, and I  
2                   guess I'm wondering, maybe you were exactly right.  
3                   Maybe the mortality signal was low, because you  
4                   managed them differently?

5                   DR. MARSHANT:   What I explained was a  
6                   concern that existed before the study started. Five  
7                   months into the study we introduced the dosing  
8                   algorithm by renal function.

9                   And by that point the steering committee  
10                  had an increased comfort level. And so when they  
11                  introduced the dosing algorithm they didn't introduce  
12                  a further dose adjustment for patients with creatinine  
13                  clearance between 40 to 60, which is why all renally  
14                  impaired patients in the Diamond AF study equivalent  
15                  to having been dosed at the 500 and dose adjusted on  
16                  renal function.

17                  DR. RYDER:   So the bottom line is that now  
18                  we have two thirds of the Diamond AF population  
19                  receiving exactly the dose that we would recommend?

20                  DR. KONSTAM:   But nobody in -- I'm sorry  
21                  to interrupt, but nobody, and correct me if I'm wrong,  
22                  nobody in Diamond in AF was started on the 500 BID

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1 dose?

2 DR. RYDER: That is correct.

3 DR. KONSTAM: So that leaves me with a  
4 problem, because that is the dose that we are going to  
5 be recommending for AF.

6 DR. RYDER: No, no.

7 DR. KONSTAM: It isn't?

8 DR. RYDER: You will be recommending that  
9 for patients whose creatinine clearance was greater  
10 than 60.

11 DR. KONSTAM: Right.

12 DR. RYDER: Fortunately --

13 DR. KONSTAM: But we don't have any  
14 patients like that in Diamond, we don't have any  
15 patients with creatinine clearance greater than 60 who  
16 are in AF, in Diamond, who were started on 500 BID.

17 DR. TEMPLE: And you would have --

18 DR. RYDER: That is correct.

19 DR. TEMPLE: -- had 85, that is how many  
20 you would have had.

21 DR. KONSTAM: We would have, but we didn't  
22 -- but we don't know how many of those 85 would have

1 died.

2 DR. TEMPLE: That is right, that is what  
3 you are missing, the 85 people who would have gotten  
4 the 500 --

5 DR. KONSTAM: Is that 85 from the  
6 treatment group, or 85 from the whole 500?

7 DR. MARSHANT: From the whole 506.

8 DR. KONSTAM: 85 from the whole 500. But  
9 I'm still left with that problem.

10 DR. MARSHANT: I'm sorry that has come up.  
11 It is 85 from the Dofetilide treated patient.

12 DR. KONSTAM: Dofetilide treatment group,  
13 so it is 85 out of about 250?

14 DR. TEMPLE: It is about one third. So  
15 you do not have that data, that is true.

16 DR. KONSTAM: The only other question I  
17 had, I mean, this is just a general question. We have  
18 some concerns, and you've addressed them, really,  
19 fairly meticulously, as far as I can see, with a  
20 strategy, and then you've implemented that strategy,  
21 we have a terrific data set.

22 But we've heard concerns from the panel

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1 about how are we going to really implement the  
2 strategy. And I guess, to me, this is going to impact  
3 on my thinking about approvability, because it is  
4 going to be contingent on saying that there is going  
5 to be some strategy here that is going to, you know,  
6 approach what you are able to achieve in the clinical  
7 trial data set with regard to dosing strategy, and  
8 with regard to having people in the hospital for five  
9 doses, or two or three days.

10 So I guess I would like to hear something  
11 from the sponsor about what your thoughts are, what  
12 would you propose that you would do, to make sure that  
13 this is the way patients are treated?

14 DR. RYDER: The dialogue on this has  
15 really just started, but it is our complete -- we have  
16 a complete commitment that the way Dofetilide was used  
17 in the clinical trials is the way that it should be  
18 used. You have to use it in the right patient and in  
19 the right way.

20 A lot of education, and perhaps some new  
21 things, Dr. Temple mentioned a few, we haven't had the  
22 chance to even discuss these in any depth, whatsoever.

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1 I would want to point out, though, that  
2 one of the things that is, I think, important for the  
3 Committee to consider is that the bulk of the Diamond  
4 data come from a very large segment of the Danish  
5 hospital base, and that as Dr. Pratt described, there  
6 was no central QTc reading done by a centralized  
7 reading center.

8 This was QTc reading done on the wards by  
9 the investigators, by the sub-investigators, and  
10 patients were dispensed bottles of medication. And  
11 these patients were elderly.

12 So in that way, although it was a clinical  
13 trial, it was not radically different, in my opinion,  
14 from some aspects of --

15 DR. KONSTAM: Well, I appreciate what you  
16 are saying, but I mean, I don't know how clinical  
17 trials are conducted in Denmark, but I still would say  
18 it is radically different from just having the entire  
19 population of clinicians in the United States  
20 prescribe the drug.

21 So, I mean, like I said, I would like to  
22 ask just Bob and Ray, because I mean, I think

1       logically the question of approvability is first, and  
2       then the question, okay, then what do we do?

3               But I guess in my own mind some sense that  
4       we are going to have a strategy of succeeding is going  
5       to impact on maybe people's views about approvability.

6               DR. TEMPLE:       There is a number of  
7       possibilities.    You could, since this program has  
8       obviously not been developed and presented to you, you  
9       could say you are not ready to reach a final  
10       conclusion until you see what it is, and that you  
11       think it is necessary.   That is one possibility.

12               You could conclude that you will leave it  
13       to the company and us to work out, but give some  
14       general guidance.

15               I mean, there are all those possibilities,  
16       and I have to acknowledge, we are heading toward new  
17       ground.   The only two examples that are worthwhile, I  
18       would say, the way Clozapine was marketed.

19               You could not get your next dose unless  
20       you show the results of a blood test.   Well, one can  
21       imagine that you would get some sort of bar code when  
22       you have your three days in hospital, and you are a

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1        bona fide guaranteed acceptable QT, and that would be  
2        the only way you could get medicine.

3                    How to do that is not known to me, but  
4        that doesn't mean it can't get done. And there are a  
5        number of possibilities of that. I mean, if you  
6        believe QTs cannot be read by most people properly,  
7        they could work out a way of reading people's QTs, as  
8        well as -- or they might, they don't have -- they  
9        might not be willing to do that, I don't know.

10                   But if you all thought those things were  
11        central, communicate that, and figure out what is  
12        essential and what is not. But there is a lot of  
13        possibilities, and we have reasonable authority, you  
14        should know this, under our accelerated approval rule,  
15        which is usually thought of as allowing approval based  
16        on the results of a reasonable surrogate for  
17        effectiveness, there is also a provision that if a  
18        drug cannot be marketed safely, without particular  
19        limitations, those limitations can be imposed.

20                   They were used to approve Thalidomide for  
21        certain exotic conditions where you definitely didn't  
22        want it spreading widely through the community.

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1           So in that case physicians are registered,  
2           there are a lot of possibilities, only imagination  
3           limits those. And to the extent you think those are  
4           important, you need to tell us. Because if they are  
5           not important, they are very burdensome.

6           ACTING CHAIRMAN CALIFF: Ray, briefly.

7           DR. LIPICKY: Well, really two comments.  
8           The first is going way back to the question about Dig,  
9           and there is an anecdote that I would like to relay to  
10          everybody that -- because I can't show you the data.

11          When Anafrodil was approved, there were  
12          Torsade reported, associated with its use. The vast  
13          majority of the Torsade that were reported with  
14          Anafrodil, were people with heart failure, who were on  
15          Dig.

16          We were told by the community at that  
17          time, not you guys, but another community, that that  
18          is commonly known, that Dig is a bad actor. We said,  
19          okay, we will find out if that is true or not, we will  
20          go to our adverse drug reaction reporting system, and  
21          pull every Torsade that ever has been reported,  
22          irrespective of why it was, and just look and see what

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1 the incidence of Dig was, in that population.

2 It was something on the order of 60  
3 percent of the cases. We haven't done anything, we  
4 are not advising doing anything, but there is some  
5 other evidence that suggests that what was seen here  
6 is true. That is all I'm saying. and so that is a  
7 little anecdote.

8 The only other very short thing is, there  
9 is another conclusion you could come to from the  
10 conclusion that Bob presented, okay? Or suggestions.

11 You could conclude that clearly this drug  
12 does something to alter the recurrence of atrial  
13 fibrillation when you are an outpatient, that it  
14 clearly does something to the QT interval. That both  
15 of those things are dose related; that the safety  
16 margin is very narrow, and that a doctor might start  
17 at some very low dose, and the patient will say, geez,  
18 my atrial fibrillation came back, I don't like that,  
19 it is too fast, jack me up a little.

20 And then, well, still a little too fast,  
21 I would like it to be about 8 months, jack me up a  
22 little. So I don't see that as -- if you believe that

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1 in fact the agent works, that its working is related  
2 to the dose and/or plasma concentration, and that the  
3 QT interval, in fact, is also related to dose and/or  
4 plasma concentration.

5 So the latitudes here are pretty enormous.  
6 But that would require doing something no one has ever  
7 done, and that is say I don't require an arm of a  
8 fixed dose trial that in fact beats placebo.

9 DR. PRATT: Could I make just one comment?  
10 Because I think it is pretty related to this Dig  
11 issue.

12 ACTING CHAIRMAN CALIFF: Quickly.

13 DR. PRATT: Would you allow one slide?  
14 Backup 23, same study, the drug interaction study,  
15 5,000 patients. This is the ECG QTc change with the  
16 present combination of Dig plus Dofetilide and Dig  
17 without Dofetilide. I don't see a signal there. I  
18 just thought you would like to know, in 2,300  
19 patients.

20 ACTING CHAIRMAN CALIFF: Now I have to  
21 make a comment. No, I won't, but I will when we get  
22 to that. Let's move to Dr. Atkinson. Do you have any

1 further questions?

2 DR. ATKINSON: Well, yes, there is a  
3 question, and that is, any time when you see a drug  
4 effect that over time loses its efficacy, if you will,  
5 and here we are talking about a 40 to 50 percent  
6 relapse rate after a year, there are a number of  
7 reasons for that.

8 One is that the drug is not working, the  
9 other is that the patient is not taking it. I wonder  
10 if you had, in your trials, any way to estimate what  
11 the role of non-compliance might have been in the  
12 recurrence rate?

13 DR. RYDER: Bradley, do you have some  
14 information on compliance? Dr. Marshant.

15 DR. MARSHANT: I don't have information on  
16 compliance, but I can tell you that the QTc difference  
17 between Dofetilide and placebo was maintained  
18 throughout the studies, so that is as good as evidence  
19 as we can get of compliance.

20 DR. ATKINSON: When the patients relapse  
21 did you check their QTc to see that they were still  
22 prolonged?



1 DR. MARSHANT: When the patients relapsed  
2 they were --

3 DR. ATKINSON: From Dofetilide, before you  
4 stopped the drug, presumably, did you measure the QTc  
5 to see if it was still prolonged?

6 DR. MARSHANT: We don't have that data,  
7 sir.

8 DR. ATKINSON: I mean, what you are  
9 proposing is that you don't need to measure blood  
10 levels because you have the QTc as a surrogate for the  
11 level, if you will. What I'm suggesting to you is  
12 that if you are going to use the QTc as a surrogate,  
13 you've got to help the physicians, because if the  
14 patient relapses they have one of two choices to make.

15 They can say, look, this is a drug  
16 failure, and I'm going to switch to Amiodarone, or  
17 they can say the dose was too low, or maybe the dose  
18 is appropriate and the patient wasn't taking the dose,  
19 and that isn't a very sophisticated way of using blood  
20 levels, but that is one of the ways that we use them.

21 So if you propose that QTc is going to obviate  
22 the use of plasma level monitoring, I would like to

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1 see some evidence that has been useful to you in  
2 looking at things like compliance.

3 DR. RYDER: Dr. Ruskin?

4 ACTING CHAIRMAN CALIFF: If it is a direct  
5 response to the question.

6 DR. RUSKIN: I think it is. I think the  
7 data that you are asking for don't exist, but I think  
8 that relapses reflect the nature of this disease  
9 process.

10 And, in fact, with every treatment option  
11 that we have available, we see relapse rates of around  
12 50 percent in a year, and even with Amiodarone, which  
13 has an infinite half life, we see recurrence rates in  
14 the range of 30 to 40 percent in a year.

15 So I think we are looking at a reflection  
16 of the biology here, of the problem, rather than an  
17 issue specifically related to Dofetilide.

18 I want to take five seconds, also, to draw  
19 an analogy. I agree with everything that is said  
20 about the concerns regarding the in-patient  
21 initiation, and the difficulties of the measurements  
22 that have to be made, but this is not an absolutely

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1 unique situation.

2 We use Sotalol every day, and Sotalol  
3 requires adjustments for renal function, and it has to  
4 be dosed according to QT interval changes. So this is  
5 not an entirely new phenomenon, it is not a perfect  
6 analogy, but it is not an absolutely unique situation.

7 ACTING CHAIRMAN CALIFF: Just a point for  
8 others developing drugs for this indication. I take  
9 it from the discussion that we would recommend that  
10 those who relapse should be looked at, and that  
11 follow-up shouldn't stop at the point of relapse the  
12 first time?

13 Does anyone on the panel disagree with  
14 that? I mean, I think that is a very important point  
15 that has arisen from these data and the discussions,  
16 is that we really wish we knew what happened to the  
17 people who had a recurrence.

18 Dr. Graboys, do you have further  
19 questions?

20 (No response.)

21 ACTING CHAIRMAN CALIFF: Okay. I think  
22 what we ought to do is then move into the questions,

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1 and it seemed -- Bob?

2 DR. TEMPLE: It is sort of related to the  
3 questions that will come.

4 Who do you think this drug is for;  
5 everybody who is fibrillating, everybody who is  
6 immobilized by its symptoms, everybody who hates his  
7 life, who, what subset.

8 DR. RYDER: Are you asking the sponsor?

9 DR. TEMPLE: Yes.

10 DR. RYDER: The type of patient who I  
11 would envision being treated is the type of patient  
12 who was enrolled in the clinical trials, and I think  
13 Dr. Ruskin summarized that in his benefit risk.

14 DR. TEMPLE: Wow, 50 percent of them  
15 weren't even symptomatic, right? You want to do that?

16 DR. RUSKIN: No, I guess I would state it  
17 a little differently, and that is that I would see the  
18 use of this drug as no different from any other rhythm  
19 control agent in atrial fibrillation.

20 And, again, I'm speaking personally now,  
21 and the indications for me would be highly symptomatic  
22 atrial fibrillation, where the risk of the therapy is

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1       outweighed by the benefit.     And that is a very  
2       difficult decision to make sometimes, but we all have  
3       patients like that, we try to reach those decisions  
4       using clinical judgement, and interaction with the  
5       patient.

6                     But the straight answer is symptomatic  
7       patients, not everybody with atrial fibrillation, by  
8       any means.

9                     DR. TEMPLE:    Just to pin that down, that  
10       is not exactly the population entered into this?

11                    DR. RUSKIN:    That's correct.

12                    DR. TEMPLE:    Nor need it have been, but it  
13       is somewhat different from the people studied.

14                    DR. KONSTAM:  -- ask Jeremy what -- could  
15       you just expand on that slightly?    So, I mean,  
16       somebody whose symptom is palpitation, but is driving  
17       you crazy and himself crazy because he has  
18       palpitation, is that, what would you do?

19                    DR. RUSKIN:    Marv, I think it is more a  
20       question of the level of functional impairment, and I  
21       think there are lots of people on the panel who could  
22       answer this question as well as I can, who see these

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1 patients.

2 The issue for me is, really, the degree to  
3 which the level of symptoms interfere with  
4 functioning, and quality of life. And that is largely  
5 an answer that one gets from the patient.

6 I think that for me the symptoms that are  
7 most troublesome, that I hear about in this  
8 population, relate to diminished effort tolerance,  
9 fatigue, dyspnea with minimal activity, in which there  
10 is a strikingly noticeable difference between atrial  
11 fibrillation and sinus rhythm.

12 DR. KONSTAM: Jeremy, would you add to  
13 that contraindications to anticoagulation, add to the  
14 group?

15 DR. RUSKIN: Well, I think certainly most  
16 clinicians would be influenced by that, that is our  
17 attempt to maintain sinus rhythm would be much more  
18 aggressive in patients who cannot take Warfarin, but  
19 we don't have evidence, definitive evidence, that  
20 suppression of atrial fibrillation with antiarrhythmic  
21 drug therapy prevents stroke.

22 It is a perfectly logical hypothesis, but

1 as you know we don't have an answer to that question.

2 ACTING CHAIRMAN CALIFF: I think we ought  
3 to move into having the panel address the questions,  
4 unless there is a non-philosophical question, but a  
5 data related question for the company, or the experts.

6 DR. GRINES: Rob, I have an  
7 electrophysiologic question, and I wonder how certain  
8 electrophysiologic experts are that QT prolongation is  
9 predictive of Torsade? Because even in this trial,  
10 even though the ECGs are monitored very closely, there  
11 still was a higher incidence of Torsade compared to  
12 placebo, even after hospital discharge.

13 And then secondly I think there are  
14 examples, in fact I think they've showed one where  
15 Digoxin did not have a longer QT, and yet there is a  
16 two-fold increase in Torsade, and I believe Amiodarone  
17 is similar, you can't necessarily use the QT interval  
18 to predict Torsade.

19 So I'm concerned about how we monitor  
20 these patients, and whether in fact, we should draw  
21 blood levels.

22 DR. KOWEY: As a sort of general answer to

1 that, and I will take a crack at it, I think that  
2 there clearly is a generic predisposition of Torsade  
3 in the population, and it is probably a genetic  
4 abnormality for which someone is hetero, rather than  
5 homogenous.

6 And I don't think that there is any way,  
7 a priori, to know who those people are. And there is  
8 always going to be a risk of Torsade without much QT  
9 prolongation in those individuals. I think that is  
10 the explanation why some people take a couple of doses  
11 of quinidine and Torsade, for that much of a change in  
12 their QT interval.

13 But I don't really see that as being a  
14 problem that is unique to this compound. It is an IKR  
15 blocker, I think we understand it, I think we  
16 understand its electrophysiology. I don't think it  
17 really -- I agree with something Jeremy said a little  
18 bit ago, which is actually a good comment, which is,  
19 it is not that far off from things that we already do  
20 with other drugs.

21 So I don't think it is really fair to hold  
22 this drug to that kind of a higher standard when we

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1 know, for a fact, that drugs that prolong the QT  
2 interval are going to have some mortality  
3 disadvantage, and they are going to have some  
4 mortality disadvantage.

5 Craig, I mean, I know I see the data, I  
6 believe the data, you did a wonderful job with it, but  
7 some people are going to die on this drug, and there  
8 is really not much we are going to be able to do about  
9 that.

10 But that doesn't make it not approvable.  
11 So I think that is where the discussion sort of has to  
12 go.

13 DR. GRINES: Well, I don't know whether we  
14 are going to talk about this issue in the questions,  
15 but I think that several members of the panel are  
16 concerned about just approving drugs for surrogate  
17 endpoints when we don't have the mortality  
18 information.

19 And, clearly, we know that antiarrhythmics  
20 have caused a higher mortality in numerous studies.  
21 And as you stated yourself, just because we were  
22 ignorant two years ago doesn't mean we have to

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1 continue to be ignorant.

2 DR. KOWEY: I don't disagree with you, I  
3 think this is the crux of the discussion that the  
4 panel is going to have in the next hour, can you see  
5 your way past a risk which is, as best as can be  
6 defined, defined.

7 I mean, I think the data base is very  
8 robust, and we have a lot of very good data, but you  
9 still have to take a leap in order to approve the drug  
10 for clinical use.

11 And the question is, can you or can't you?  
12 And you have to answer your conscience, I guess. It  
13 is a tough call.

14 DR. GRABOYS: That is part of the problem.  
15 We are looking for a hook to hang some help to define  
16 vulnerability to death, and when we used to call  
17 antiarrhythmics as poisons with desirable side  
18 effects, which the traditional -- the reality is, 15  
19 years ago we looked at 1A agents and couldn't find any  
20 relationship between QT prolongation and risk of  
21 Torsade, or even prime RVF in that case, and levels  
22 were no help.

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1           Levels were helpful if the patient had a  
2 recurrence, and you took a level and you didn't find  
3 it, that was helpful. But otherwise it was not  
4 helpful in predicting. And that is part of the  
5 concern, I think, that we all have in terms of the  
6 approving of this drug.

7           DR. GRINES: As a follow-up to Bob's  
8 question, as to whom would you give this drug to, if  
9 you look at the Diamond population in the heart  
10 failure world, there would be probably two reasons  
11 that you would want to get somebody out of afib, one  
12 would be to improve their output, and the second would  
13 be hoping that if there is a rate related  
14 cardiomyopathy, that if you can restore sinus rhythm  
15 and control rate, that some of the ventricular  
16 dysfunction will improve, which we've seen.

17           However, in that case, would you perhaps  
18 not chose Amiodarone since some people think that  
19 there is actually a mortality protection, and it is  
20 currently being studied.

21           DR. BIGGER: Well, I'm just going to  
22 respond to the point that Cindy is bringing up. I

1 think actually in the sponsor's data, and gathered by  
2 their investigators, they started to adjust for  
3 creatinine clearance, and the QT interval response to  
4 the drug, they had a substantial drop in the rate of  
5 Torsade.

6 And I think that is -- it is not perfect,  
7 but it is relatively direct evidence that this  
8 algorithm does work to some extent. It is better than  
9 not adjusting, for sure.

10 ACTING CHAIRMAN CALIFF: I think this is  
11 going to be the key. Well, you are right, it is not  
12 directly addressed in the questions. I guess we ought  
13 to have this discussion now.

14 DR. GRINES: Well, I just have some  
15 concern because if you compare this to a thrombolytic,  
16 which has a rate of intracranial bleeding that is very  
17 close to the rate of Torsade after hospital discharge,  
18 we would not approve it on a sample size like this.

19 And so I don't understand what the  
20 difference is, and I guess I'm not convinced that the  
21 data base is as robust as -- I don't know, it just  
22 doesn't seem like we have enough patients to answer

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1 some of the important questions.

2 ACTING CHAIRMAN CALIFF: Well, maybe I  
3 could give a little different perspective, because I  
4 think it is the number of -- and there is a  
5 subselection here, in my opinion, that is a difficult  
6 issue.

7 But it is really the number of deaths and  
8 not the number of patients that is the critical thing  
9 to look at in terms of sample size.

10 And we have a data base with eleven  
11 hundred and something deaths. And the subselection  
12 issue, which I grant you is a very difficult one, most  
13 of the deaths are not in the primary atrial  
14 fibrillation population, so there is a difficult issue  
15 there.

16 The 1,100 deaths is not far removed from  
17 what you would see in a large thrombolytic trial where  
18 the mortality rate is substantially lower, admittedly  
19 again, over a shorter period of time.

20 And I think your analogy, though, is a good  
21 one, and I was thinking the same thing with regard to  
22 cardiac surgery, for example, or percutaneous

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1 intervention, where the issue is not do you  
2 occasionally create harm, because that happens with  
3 all those treatments.

4 The issue is, on balance, does the harm  
5 that you create outweigh the potential benefit? And I  
6 think that is what we have to struggle with. It does  
7 concern me to focus just on the risk of Torsade,  
8 because we send people to surgery every day, we -- you  
9 know, even beta blockers, which we use very commonly,  
10 we know reduce mortality, do occasionally create  
11 substantial harm.

12 So that is what -- I know that is what we  
13 are struggling with.

14 Bob?

15 DR. TEMPLE: I think you are slightly  
16 talking past each other in one way. Dr. Grines is  
17 basically saying there aren't that many people with AF  
18 that have been treated.

19 You are obviously counting the results of  
20 the other study, which is huge, and has a large number  
21 of deaths, rather than any thrombolytic trial that I  
22 know about, by the way.

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1           So there is a discontinuity there. Are  
2 both equally relevant to this, or are they not? And  
3 I think you haven't met on that question yet.

4           ACTING CHAIRMAN CALIFF: One way of  
5 approaching this would be to have a question 1D, which  
6 would allow us to discuss, more formally, the  
7 tradeoff.

8           I think the question 1 is really oriented  
9 towards the benefits in the prevention of the  
10 recurrence of atrial fibrillation. If we felt that  
11 the evidence was not there for question one, then we  
12 could essentially stop at that point.

13           But if the answer to 1A, B, and C, is  
14 positive, then we have to come back to a discussion of  
15 how does that weigh against the risk.

16           So what I would like to do is to move  
17 right into question 1, and come back to the -- how do  
18 we balance, if the answer to that is positive, against  
19 the risk that we've seen.

20           So question one: Is Dofetilide superior  
21 to Placebo in terminating -- and there is a  
22 tantalizing converting in parentheses -- episodes of

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1 atrial fibrillation. If so how strong is the  
2 evidence?

3 Peter, if you could start?

4 DR. KOWEY: I think the answer to that  
5 question is yes, and I think there is enough data, my  
6 opinion is there is enough data from studies 345 and  
7 120, in a placebo control fashion to answer the  
8 question positively.

9 So I would say yes to that.

10 ACTING CHAIRMAN CALIFF: Cindy?

11 DR. GRINES: Well, my answer would also be  
12 yes in the basis of two trials showing approximately  
13 a 30 percent rate of conversion, but I have to  
14 question its clinical relevance because, clearly, with  
15 electrical cardioversion you have a higher rate, and  
16 it is faster, and potentially less expensive.

17 ACTING CHAIRMAN CALIFF: Tom, if we could  
18 start with you and come back around?

19 DR. GRABOYS: I'm in concert with Cindy  
20 and Peter. Yes.

21 DR. KONSTAM: Marvin?

22 DR. KONSTAM: I will say yes. I guess I

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1 will point out that the obvious -- that there is not,  
2 we don't have a study that was specifically designed  
3 with this as the primary endpoint. So we don't have  
4 that.

5 So we have to sort of say, okay, based on  
6 what we have. But I think the data in the trials that  
7 we have are pretty strong, so I will say yes.

8 ACTING CHAIRMAN CALIFF: Tom?

9 DR. BIGGER: Yes.

10 ACTING CHAIRMAN CALIFF: Ileana?

11 DR. PIÑA: Yes.

12 DR. D'AGOSTINO: I agree, but I think we  
13 do have strong data, I think it is secondary, but it  
14 is quite consistent and quite striking. I mean, here  
15 is the case where the foreseeable rate is extremely  
16 low, and by the time you get to the higher regiment,  
17 or at least one that starts off at a higher dose you  
18 have a fairly substantial conversion rate.

19 So I definitely say yes.

20 ACTING CHAIRMAN CALIFF: Joan?

21 DR. LINDENFELD: Yes.

22 DR. KOWEY: Can I just ask one

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1 clarification? Do we have a breakdown for fib and  
2 flutter in that percentage? It is 29 percent in -- or  
3 30 percent, as Cindy said. Was it substantially  
4 higher for flutter?

5 DR. RYDER: We do have that segregation,  
6 and I guess the numbers are going to be retrieved, but  
7 it is higher for flutter.

8 ACTING CHAIRMAN CALIFF: I would vote yes,  
9 too, on 1A.

10 1B I guess I would like to ask, in the  
11 sense of -- the question is, to what extent does the  
12 evidence consist of data from dosing regimens no  
13 longer recommended by the sponsor?

14 Maybe there should be a graded response  
15 here, and I know Marvin brought this up. Either a lot  
16 and it is concerning, a lot and it is not concerning,  
17 or not much. Those would be the three options.

18 DR. KONSTAM: I'm not sure I raised the  
19 concern about with regard to efficacy.

20 ACTING CHAIRMAN CALIFF: Okay, Peter,  
21 maybe you can --

22 DR. KOWEY: I don't think it is a problem.

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1 I don't think there is much of it, and 345 was a study  
2 done completely after the creatinine shifted, or the  
3 creatinine clearance adjustment was made.

4 And 120 was substantially within that time  
5 frame. So I don't have a problem with the data.

6 ACTING CHAIRMAN CALIFF: Bob?

7 DR. TEMPLE: Do I remember correctly, the  
8 conversion rates at the two lower doses were trivial,  
9 so it really is only the higher dose that has anything  
10 going for it at all, here, right?

11 DR. RYDER: That is correct. The numbers  
12 for the 250 and 125 were low. And we do have the  
13 numbers, Dr. Califf, for flutter and fib.

14 DR. MARSHANT: Yes. For the pool across  
15 120 and 345, for fibrillation there were 46 out of 179  
16 patients on the 500 mg dose converting, which is 26  
17 percent, compared to one percent placebo rate. And  
18 for flutter it was 15 out of 27, which is a 56 percent  
19 conversion rate.

20 DR. KOWEY: So the numbers are lower, but  
21 proportionately higher?

22 DR. MARSHANT: Compared to a placebo rate

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1 of three percent.

2 DR. KOWEY: So the number I heard was  
3 about 28 percent for fib, and about 56 percent of  
4 flutter, which is pretty much in the frame of what  
5 we've seen with other class III drugs, so it is sort  
6 of in the same ballpark, proportionately.

7 ACTING CHAIRMAN CALIFF: Okay. Does  
8 anyone in the panel disagree with Peter? Then we will  
9 move along.

10 Is conversion from AF to sinus rhythm of  
11 self-evident benefit, if not are there data to show  
12 that symptoms are reduced, or that irreversible harm  
13 was averted?

14 DR. KOWEY: I'm going to put -- I want to  
15 make sure that the panel understands that when I  
16 answer this question I'm doing it with a clinician's  
17 hat on, and not a regulatory hat, because I can tell  
18 you that categorically, that most physicians want to  
19 have their patients restored to normal sinus rhythm.

20 And the reality is that they are going to  
21 do it. They are going to do it specially in patients  
22 who have the kinds of symptoms that Jeremy outlined

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1 earlier.

2 So that, although I think the data in this  
3 application are not compelling with regard to  
4 symptoms, I think the data are going in the right  
5 direction. The directionality isn't bad.

6 It is not as compelling as I would have  
7 liked it to be, there certainly wasn't a primary  
8 endpoint anywhere in the trial.

9 And it is a benefit to many of the  
10 patients who are in these trials. So I would give  
11 this a weak yes. But I would give it a yes, without  
12 a whole lot of enthusiasm, but I do give it a yes.

13 DR. GRABOYS: I'm really underwhelmed in  
14 this regard. First of all, I think there is a huge  
15 placebo effect with atrial fibrillation. In other  
16 words, patients come in, they are in AF, they hear the  
17 word fibrillation, they think they are going to have  
18 a cardiac arrest, they are sure they are going to have  
19 a stroke. A well meaning doc points it out, you have  
20 atrial fibrillation, they never had a symptom before,  
21 now they have symptoms all the time.

22 And when I was looking at the quality of

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1 life question, there, again I was underwhelmed by  
2 that, because I think as a physician we can deal with  
3 these patients, very often, and decompress them  
4 psychologically.

5 So I'm under, underwhelmed. Yes.

6 ACTING CHAIRMAN CALIFF: Cindy?

7 DR. GRINES: I just want to clarify that  
8 they are talking, and question 1C is just about the  
9 acute conversion.

10 ACTING CHAIRMAN CALIFF: Yes.

11 DR. GRINES: And actually there is zero  
12 data that I saw that acute conversion alters symptoms.  
13 The only data that were provided were one month  
14 quality of life, to my recollection.

15 ACTING CHAIRMAN CALIFF: But the first  
16 question there is, is acute conversion of self-evident  
17 benefit.

18 DR. GRINES: No, I don't think we have  
19 data to support that, and I don't think the sponsor  
20 provided any information about the acute conversion.

21 ACTING CHAIRMAN CALIFF: Bob?

22 DR. TEMPLE: Well, I'm looking at -- that

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1 is a slightly weird question, because nobody is going  
2 to use --

3 ACTING CHAIRMAN CALIFF: We've gotten used  
4 to those.

5 DR. D'AGOSTINO: Yes. Nobody is going to  
6 use it to convert acutely, the point is to convert  
7 this way, as opposed to with cardioversion, and then  
8 keep people on the drug. So the real question is  
9 whether long-term suppression is a self-evident --

10 DR. LIPICKY: But that is not what this  
11 question was about.

12 DR. TEMPLE: What is it asking?

13 DR. LIPICKY: -- terminating AF.

14 ACTING CHAIRMAN CALIFF: That is question  
15 2, that is the next question.

16 DR. TEMPLE: Well, but is the question --

17 DR. LIPICKY: So if someone is in AF --

18 DR. TEMPLE: Right.

19 DR. LIPICKY: Is it self-evident they  
20 shouldn't be? That is exactly what the question was  
21 meant to ask.

22 DR. TEMPLE: That still seems a funny

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1 question, because the people contemplating this are  
2 planning to convert one way or another, and then  
3 maintain the patient, otherwise what is the point?

4 So maybe --

5 DR. LIPICKY: Well, but that was what was  
6 being asked. I know everyone is going to cardiovert.  
7 Why? Is it self-evident that you should be in sinus  
8 rhythm?

9 DR. TEMPLE: To me that question comes up  
10 when you ask about maintenance.

11 DR. LIPICKY: If it is self-evident, if it  
12 is not self-evident you should be in sinus rhythm, why  
13 does everyone cardiovert?

14 DR. TEMPLE: That is the maintenance  
15 question.

16 DR. LIPICKY: And that is what this  
17 question was asking.

18 DR. TEMPLE: It is still a dumb question.

19 DR. LIPICKY: Okay.

20 DR. GRINES: Well, I am not convinced that  
21 everybody cardioverts. I mean, maybe the  
22 electrophysiology people see a different patient

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1 population. But in my clinic there is lots of people  
2 in afib who nobody has ever tried to cardiovert.

3 And you know I guess I'm not convinced  
4 that, for example, if you ask the question, is  
5 chemical cardioversion better than electrical, I don't  
6 think that we have any information on that.

7 ACTING CHAIRMAN CALIFF: So what I would  
8 like to do is just specifically answer the question.  
9 It may be very quick, it may be no and no for  
10 everybody else in the panel. I heard Peter give a  
11 lukewarm yes, it is self-evident benefit.

12 Marvin?

13 DR. KONSTAM: I am going to answer yes to  
14 the first part of that question, after taking the  
15 liberty to modify a little bit.

16 You know, I think the thing is that you  
17 can't -- first of all, I think it is sort of what Bob  
18 was saying, you can't talk reasonably about  
19 maintaining sinus rhythm until you cardiovert.

20 I think you can get into -- clearly, as  
21 the sponsor pointed out here, if there is an  
22 advantage, which is debatable, it is that a third of

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1 the patients are spared the shock.

2 I mean, I guess that is really the thing.  
3 And one could debate whether that is a good thing or  
4 not, but that is the thing. You know, I read the  
5 question more a question of is it a good thing to be  
6 in sinus rhythm independent of whether or not you can  
7 demonstrate symptom improvement.

8 And I am skeptical that the sponsor's  
9 clearly demonstrated symptom improvement, but I'm not  
10 too worried about that, because I think it is self-  
11 evident that there is a sizable population that will  
12 benefit from being in sinus rhythm. I think being in  
13 sinus rhythm is a good thing.

14 So that is a modification. I will say  
15 yes.

16 ACTING CHAIRMAN CALIFF: One other  
17 interpretation of this, at least that I'm taking,  
18 which is that if you are going to be developing  
19 evidence for evidence based medicine, or trying to  
20 develop a new therapy, would it be enough to simply  
21 show that you caused a higher rate of conversion, or  
22 would you need to show that you improved symptoms?

1 DR. KONSTAM: Can I just say -- I mean, I  
2 think that the higher rate of conversion would be  
3 meaningless if you didn't also demonstrate maintenance  
4 by some method. So let's just say that.

5 But I think with regard to the question  
6 that you are asking, I think the problem with  
7 insisting on demonstrating symptom improvement is that  
8 we don't know how to show it, all right?

9 We really do know whether somebody is in  
10 sinus rhythm or atrial fibrillation. And given that  
11 I'm willing to take liberties with saying, and it is  
12 really based on some of the things that Jeremy said,  
13 that there are sizable populations of patients that we  
14 know, as clinicians, are going to be better off in  
15 sinus rhythm than atrial fibrillation.

16 ACTING CHAIRMAN CALIFF: Tom?

17 DR. BIGGER: They didn't have a lot of  
18 evidence for drawing on personal experience. There  
19 are a lot of people who decompensate and have a --

20 ACTING CHAIRMAN CALIFF: You are going to  
21 have to keep pressing your button, it turns off  
22 automatically, like on the slide projectors.

1 DR. BIGGER: -- get better when they are  
2 converted, and they get better reasonably quickly. So  
3 there must be some in here, it is just that it could  
4 have been much better documented, for sure.

5 DR. PIÑA: I don't think that my goal to  
6 convert people to sinus rhythm necessarily has  
7 anything to do with symptoms, but it has to do with  
8 the far reaching effects of being in atrial  
9 fibrillation, which I think we are leaning more toward  
10 that is not a good thing.

11 So I would have to say yes for the first  
12 part, and I'm not convinced about any symptoms in  
13 this, at all, so I would have to say no for the second  
14 part.

15 DR. D'AGOSTINO: I'll say no based on the  
16 day-to-day presented.

17 DR. LINDENFELD: I'll say no to both. I  
18 think it is likely that people benefit, but I just  
19 haven't seen evidence that makes me sure that is so.

20 ACTING CHAIRMAN CALIFF: And I would also  
21 say no to both, but I also believe it would be very  
22 easy to demonstrate, if you just ask people how do you

1 feel right before hand, and how do you feel right  
2 afterwards, that you could pretty easily show a  
3 symptom benefit.

4 DR. LIPICKY: But that is what they did  
5 here, and they didn't -- and you say you are not  
6 convinced they found it?

7 ACTING CHAIRMAN CALIFF: No, no. They  
8 didn't do it for acute conversion. That would be a  
9 question you would ask five minutes before and ten  
10 minutes after, and there would be a big difference.

11 Now we get to the maintenance, which is,  
12 I think, the issue you are raising. I'm presuming,  
13 based on the discussion we've had so far, that for 2A  
14 everyone agrees that the evidence is strong, because  
15 we've been through that with regard to acute  
16 conversion.

17 And for 2B, is there anyone who feels  
18 differently than they did for the question above?

19 (No response.)

20 ACTING CHAIRMAN CALIFF: So we really come  
21 to 2C, is deferral of relapse into atrial fibrillation  
22 of self-evident benefit? And if not, if you answer

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1 yes to that then you are saying that there are two  
2 trials here that show a clinical benefit.

3 We have yet to discuss the other side of  
4 the equation, which would be next. If you answer no  
5 to is it a self-evident benefit then are there data to  
6 show that symptoms were reduced, or that irreversible  
7 harm was averted?

8 Peter?

9 DR. KOWEY: As I -- the first one I  
10 answered more towards the first part, and less to the  
11 second part. This one I will do the opposite and say  
12 that I'm less convinced that over the long term,  
13 specially since there is a risk over the long term of  
14 toxicity, and for the reasons that Tom brought up  
15 earlier, talking about people getting diuretics, or  
16 getting diarrhea, becoming hypokalemic, taking other  
17 drugs, specially other drugs.

18 We are exposing patients to a longer  
19 period of time in -- with a risk of an adverse effect.  
20 So it is not as self-evident that it is a benefit,  
21 because of the potential -- I think because of the  
22 potential risk. That is my opinion.

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1           However, it isn't the question exactly,  
2           Marv, but it is really clinically important, and I  
3           think it is the way I'm going to answer it, so you can  
4           answer it the way you want to.

5           But the second part of it I feel a little  
6           more strongly about. I think that they do have some  
7           data in here that suggests that patients did feel  
8           better, and did fare a little bit better, and felt a  
9           little bit better, and could do a little bit more.

10           So that I think the data for -- it is less  
11           self-evident, but the data support the claim a little  
12           bit better for this part of the question than for the  
13           other part.

14           DR. GRINES: Was that a yes or a no?

15           DR. KOWEY: It was a very lukewarm yes,  
16           mostly for the second part of the question.

17           DR. GRINES: Okay. You know this one is  
18           a little more difficult. I agree in large part with  
19           what Peter said, but I have numerous concerns. One of  
20           them is that this wasn't the primary endpoint of any  
21           trial.

22           The second thing is if you look at some of

1 the FG reviewers comments, these weren't pre-specified  
2 endpoints. You know, there is some question on how to  
3 interpret that, none of the P values were adjusted for  
4 multiple times of measurements.

5 And, you know, I guess I don't know why we  
6 are only shown the data one month, when in fact the  
7 endpoint to these trials were six months or twelve  
8 months.

9 And the question comes up, is there no  
10 benefit, no symptomatic improvement at that time?  
11 Because even at one month there is only a few things  
12 that appear to be significant.

13 So I'm not entirely convinced that it has  
14 been shown, based on the treatment received, that  
15 there is a huge improvement in symptoms.

16 The second thing I think is very dangerous  
17 to draw assumptions that just because they are in  
18 atrial fibrillation they are going to be better of  
19 without it. We have numerous examples of trying to  
20 improve ejection fractions, trying to suppress PVCs  
21 where we harmed patients.

22 And I don't think we can just leap to

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1 those conclusions. So I guess my answer would be no.

2 ACTING CHAIRMAN CALIFF: Tom?

3 DR. GRABOYS: No, to both.

4 ACTING CHAIRMAN CALIFF: Bob, you had a  
5 comment?

6 DR. TEMPLE: I just want to be sure people  
7 address this. I didn't think that some of the people  
8 who thought that there were obvious benefits from  
9 being in normal sinus rhythm thought that because of  
10 anything they saw in the data base here.

11 And this data base didn't even enter  
12 symptomatic people, so it is very suboptimal for  
13 trying to show that. I just want to be sure that  
14 people address the question, for example, Jeremy said  
15 he thought it was just obvious everybody knew that  
16 there were some people who did badly.

17 Now, if nobody agrees with that, we need  
18 to know it. But that is more the basis for concluding  
19 that it is worthwhile to keep people in sinus rhythm,  
20 I would argue, than anything that is in here.

21 And so we need to know whether you think  
22 that is a credible argument, or not.

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1 DR. GRINES: Well, I guess I'm confused as  
2 to what is an acceptable endpoint, because I've sat on  
3 this committee for a few years now, and have been told  
4 that surrogate endpoints don't count, you have to have  
5 a clinical benefit that people agree on, and not only  
6 has this trial not shown a clinical benefit, we are  
7 being asked to just give our thoughts on whether we  
8 think this is an okay surrogate with no data to  
9 support it.

10 DR. TEMPLE: Surrogate endpoints can be  
11 used in drug approval, and are. Drugs for life  
12 threatening ventricular arrhythmias, for example, have  
13 historically been approved on endpoints that nobody  
14 would consider definitive. Maybe one of these days  
15 now that we have defibrillators that will change, but  
16 it certainly didn't change in the past.

17 There is some judgement in this. If, for  
18 example, you all believe with your experience that it  
19 was obvious that there were some people who feel much  
20 better when they are in sinus rhythm, you might not  
21 believe that, that is okay, too.

22 But if you believe that, that could make

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1 the ability to stay in sinus rhythm longer a credible  
2 endpoint. It is a judgement, and you are certainly  
3 free, under the Food Drug and Cosmetic Act to make  
4 that kind of judgement.

5 DR. GRINES: Well, I guess I didn't  
6 interpret the question that way. So if the question  
7 is truly do some people feel better in sinus rhythm,  
8 then I would have to say yes.

9 ACTING CHAIRMAN CALIFF: Well, the first  
10 question is, is it self-evident, independent of any  
11 data you've seen regarding this particular drug, that  
12 going into sinus rhythm is beneficial.

13 DR. GRINES: The answer to that is no.

14 ACTING CHAIRMAN CALIFF: Okay, so I think  
15 you've answered it.

16 DR. GRINES: Yes.

17 ACTING CHAIRMAN CALIFF: Marvin?

18 DR. KONSTAM: I see this as a somewhat  
19 theoretical question, and I guess it depends on how  
20 you construct it. And it seems like there are two  
21 issues to me about it.

22 One is, you know, I guess is the

1 conversion to AF a reasonable efficacy surrogate. And  
2 I guess then the question is, certainly in the end of  
3 the day, in terms of deciding on fibrillity, for  
4 example, you are going to look at cost and benefit,  
5 and I see this, really, as a benefit question,  
6 exclusively.

7 So I'm going to not think at all about  
8 adverse effects that the drug is causing. And so I  
9 will say, in those -- really that is the way I'm  
10 addressing this question.

11 I guess the next question that has to be  
12 asked is, what are -- are you saying uniformly in all  
13 patients, or are you saying, are you pretty confident  
14 that there is a population of patients that barring  
15 adverse things going on, are better off in sinus  
16 rhythm.

17 And I think the answer to that is yes.  
18 And so taking this purely as an efficacy question, and  
19 saying that it doesn't necessarily apply to the entire  
20 population of patients with AF, but certain subsets of  
21 population, I think the answer to the first part is  
22 yes.

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1 ACTING CHAIRMAN CALIFF: Tom?

2 DR. BIGGER: Before I heard all this I had  
3 an answer, and nothing I heard changed my mind, so I'm  
4 just going to put it forward.

5 I wrote down in some, even many patients  
6 the answer is yes, in my opinion, for the first part  
7 of the question. I thought there was some data in  
8 this data set to support that symptoms were reduced,  
9 but I didn't think it was very -- you know, it was  
10 powerful.

11 ACTING CHAIRMAN CALIFF: Ileana?

12 DR. PIÑA: I am going to be consistent and  
13 say yes for the first part, and again, I'm not  
14 overwhelmed with the reduction of symptoms, so I would  
15 have to say no for the second part.

16 ACTING CHAIRMAN CALIFF: Ralph?

17 DR. D'AGOSTINO: Let me go back, just  
18 briefly, to 2A, because I think we all said it was  
19 strong data, strong evidence. But I think that they  
20 do have the two studies, we are not sneaking by on a  
21 single study.

22 I think that the way they put together

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1 this, I can study the 120 was a mistake, and I think  
2 the way -- a perfectly correct position to say that  
3 they should have analyzed it like the 345, and that  
4 gives them the two positives. We aren't changing our  
5 rules.

6 As far as the 2C, I think the -- I think  
7 it is self-evident, and based on this data I think it  
8 is no. But, I mean, for example, at Framingham we  
9 spent a lot of time worrying about AF and looking,  
10 going in and out of AF, and I think that the longer  
11 you can keep them out, the better it is not going to  
12 be. It is not in this data base, but I definitely do  
13 think that there is a self-evident aspect to it.

14 ACTING CHAIRMAN CALIFF: Joan?

15 DR. LINDENFELD: I think the first answer  
16 would be yes, but I'm not at all confident that I know  
17 how many patients that is, if it is a very small  
18 number, and I suspect that it is a small number, where  
19 there is a very clear benefit. And the second part is  
20 no.

21 ACTING CHAIRMAN CALIFF: Dr. Ryder, you  
22 can go ahead and sit down if you are more comfortable

1 sitting down, because we are not going to ask you any  
2 more questions, I don't think.

3 DR. LIPICKY: The time between recurrence  
4 of AF was detected here because people became  
5 symptomatic, and then they were documented to have AF.  
6 Now, not all of the patients in the trials, that end  
7 point did not mean that for all of the patients in the  
8 trials.

9 Some of the patients were found to have AF  
10 on a routine visit. But part of the signal that one  
11 saw, in fact, was because before the interval of time,  
12 the patients weren't having any symptoms.

13 So, you know, for the paroxysmal atrial  
14 tachycardias we take pushing the button to send an ECG  
15 when you have symptoms as being a symptom driven  
16 endpoint.

17 So I want to be sure that you know what  
18 the end points were when you say that I'm not so sure  
19 that symptoms were effected here, and that we are  
20 simply dealing with a surrogate.

21 I just want to be sure you know what you  
22 are saying, because I've heard the word surrogate many

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1 times, and although this has a surrogate quality, it  
2 isn't all surrogate.

3 ACTING CHAIRMAN CALIFF: Right. So I  
4 think my vote would be yes, and no. I'm sorry, no and  
5 no. But let me explain.

6 I think we all agree that, there has been  
7 unanimous agreement by the panel that there is strong  
8 evidence that this drug prevents recurrence of an ECG  
9 finding.

10 And what you are pointing out, Ray, is  
11 that the ECG finding is detected sometimes because it  
12 shows up in a routine clinic visit, and sometimes  
13 because the patient feels bad and comes in to get  
14 checked out.

15 And I think that on the C part of the  
16 questions, I think there is disagreement and confusion  
17 that, at least in my estimation, reflects the true  
18 status of the clinical world, which is that some  
19 people feel strongly that every patient should be put  
20 in sinus rhythm, and some feel that it is a waste of  
21 time to try to do it.

22 And I think that these particular studies



1 were not very helpful in sorting that out because that  
2 was not how they were designed.

3 And I think that accurately reflects the  
4 point of view of the panel. Bob?

5 DR. TEMPLE: Marv, in answering, said I  
6 think, obviously a lot of people it doesn't make any  
7 difference, but there is a subset of people in whom it  
8 does.

9 Do the people who said no here explicitly  
10 disagree with that, or do they think it is not well  
11 defined, or what is the nature of this? There seems  
12 to be a -- we've heard two different things. I just  
13 want to be sure the issue is joined.

14 DR. GRINES: Well, I disagreed because I  
15 didn't see any data looking at a subset of patients  
16 that had symptoms that were strong enough that they  
17 had perfunct benefit from being cardioverted.

18 And the second thing is, you know, I'm  
19 just not convinced that treating an ECG abnormality,  
20 in and of itself, is of clinical benefit to the  
21 patient, it may be of some harm, based on some other  
22 antiarrhythmic trials.

1 DR. TEMPLE: Well, that a sure certainty.  
2 If someone is asymptomatic, and you put them on a drug  
3 that might produce an abnormal rhythm that is  
4 dangerous, those people would be harmed.

5 But, still, when Marv says that, there is  
6 some people -- and Tom says, there is some people who  
7 plainly are discomforted by this.

8 Do you think that is not true, you are  
9 worried that the drug can't be restricted to those  
10 people, what is the nature of it?

11 DR. GRINES: I don't think that we --

12 DR. TEMPLE: We heard two opposite things.

13 DR. GRINES: I just don't think that the  
14 studies that were designed showed me that data. That  
15 if you take a symptomatic population they fare better,  
16 or if that symptomatic population, maybe they have  
17 more side effects from the drug.

18 I mean, basically it was relatively  
19 asymptomatic population that was tested. And a lot of  
20 the data that people have quoted along the table, like  
21 the Framingham study, either personal experience, it  
22 might be related to the substrate of the patient. I

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1 mean, older patients, hypertensives, LVH, etcetera,  
2 they have atrial fibrillation, and they are going to  
3 do more poorly because of the substrate, perhaps.

4 And it is not that the rhythm, per se, is  
5 giving them a higher mortality, or more symptomatic  
6 problems. They have an underlying problem to start  
7 with.

8 DR. TEMPLE: I don't mean mortality but --  
9 okay, I think I heard you.

10 ACTING CHAIRMAN CALIFF: Okay. What I  
11 think might work would be to do question 3 and  
12 question 4, and then come back to the -- actually  
13 never asked in here, how do we weigh the two, and I  
14 think we should do that after question 4.

15 Does Dofetilide cause significant side  
16 effects other than QT prolongation and Torsade.  
17 Peter?

18 DR. KOWEY: No, I don't think we have seen  
19 anything else that is really terribly important.

20 ACTING CHAIRMAN CALIFF: Cindy?

21 DR. GRINES: I agree.

22 ACTING CHAIRMAN CALIFF: Does anyone

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1 disagree?

2 (No response.)

3 ACTING CHAIRMAN CALIFF: Okay, so we are  
4 unanimous. The only side effect or safety issue is  
5 the proarrythmic risk, and the questions is asked, are  
6 the proarrythmic hazards of Dofetilide affected by the  
7 presence of other factors, namely structural heart  
8 disease, active ischemia, and LV dysfunction.

9 It seems like it might be better just to  
10 go down the line and ask people for their  
11 interpretation of the analyses that we've seen,  
12 because there are other factors that were analyzed in  
13 addition to these three. Peter?

14 DR. KOWEY: I want to just say I think  
15 that it was a very good job of analyzing the data  
16 base. The problem is, as has been pointed out  
17 repetitively all through the day, that when you are  
18 dealing with a relatively small number of events, of  
19 true cases of proarrythmia it is very difficult to  
20 define factors which may be the most important in  
21 predicting which patients are going to have those  
22 things happen to them.

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1           And it is all, obviously, defined in terms  
2 of probability. But I'm reasonably satisfied, and it  
3 is consistent with what we have seen with other drugs  
4 that, yes, in fact these things, left ventricular  
5 dysfunction and structural heart disease are  
6 important.

7           The active ischemia part is very  
8 difficult, because the only data we really have are  
9 data that are probably not adequate to the task. And  
10 no one has really ever studied this. I mean, nobody  
11 runs around giving patients with active ischemia  
12 antiarrhythmic drugs.

13           The only experience I ever saw with that  
14 was intravenous Amuterine, and it wasn't really, it  
15 wasn't ever sorted out that way, but we did get  
16 patients with active ischemia iviamerine and we do it  
17 now.

18           But I don't think we can answer B,  
19 honestly. I think it is a non-answerable question.  
20 But I think we can say, for A and C, that there is  
21 reasonably good data that, yes, the hazards are  
22 increased by those factors, and other factors that

1 have been defined, that we don't have to go through.

2 ACTING CHAIRMAN CALIFF: Cindy?

3 DR. GRINES: I agree.

4 ACTING CHAIRMAN CALIFF: Tom?

5 DR. GRABOYS: I don't know how you can not  
6 agree. Structural heart disease and LV dysfunction,  
7 I think the sponsor, also, was referring to active  
8 ischemia as post-MI, but I think that when we are  
9 talking about proarrythmia which is actually the  
10 umbrella which Torsade comes under, we are talking  
11 about all different forms of proarrythmia, then I  
12 think that this drug could have provoked proarrythmia  
13 in a setting of structural heart disease, post-MI, and  
14 LV dysfunction.

15 ACTING CHAIRMAN CALIFF: Marv?

16 DR. KONSTAM: Yes, you know, I agree. I  
17 just want to say, more strongly, we don't have any  
18 information about active ischemia. I think the point  
19 about the Diamond MI trial doesn't really help me all  
20 that much.

21 ACTING CHAIRMAN CALIFF: Tom?

22 DR. BIGGER: I agree. The power is very

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1 low to get any kind of definitive answer, or estimate  
2 any fixed size, or anything like that. But it is  
3 pretty suggestive that structural heart disease and LV  
4 dysfunction were important.

5 ACTING CHAIRMAN CALIFF: Ileana?

6 DR. PIÑA: I agree.

7 ACTING CHAIRMAN CALIFF: I agree.

8 DR. LINDENFELD: I do too.

9 ACTING CHAIRMAN CALIFF: So I think the  
10 summary is that the panel was impressed with the  
11 analyses that were done given the data that was  
12 available, that factors were identified, gender was  
13 another one, and multiple possible drug interactions  
14 as being factors.

15 If the vote was to approve, that there  
16 would have to be considerable work to figure out how  
17 to get those into the label, and into the training.

18 DR. LIPICKY: Just to be sure I understand  
19 the answer to the question, could you give me one  
20 piece of data that says that structural heart disease  
21 increases the incidence of Torsade in this data base?

22 DR. GRINES: The only data I know is from

1 the Diamond study, where they actually looked at the  
2 CHF, and did a --

3 DR. LIPICKY: And the presence of CHF  
4 increased the incidence of Torsade?

5 DR. GRINES: Right.

6 DR. LIPICKY: That is what you said?

7 DR. GRINES: Right. And that is all.  
8 There is nothing about -- a few of the studies looked  
9 at the ideology of atrial fibrillation, and some of  
10 them had valve disease, left atrial enlargement, but  
11 I didn't see any analysis based on the  
12 echocardiographic findings.

13 ACTING CHAIRMAN CALIFF: I interpreted  
14 what most panel members are saying is that they would  
15 prefer to emphasize the factors that came out in the  
16 analysis that was done as being the key factors to be  
17 considered.

18 DR. LIPICKY: Well, for most  
19 antiarrhythmics the instructions for use say don't  
20 give to anybody with structural heart disease. Is  
21 that what you want to end up saying here?

22 ACTING CHAIRMAN CALIFF: But I think that



1 is a different issue, because that involves a total  
2 assessment of the risk benefit.

3 DR. LIPICKY: What you have said, right  
4 now, is that you have identified in this data base,  
5 the fact that the adversity of Dofetilide increases in  
6 people who have structural heart disease compared to  
7 people who do not.

8 DR. GRINES: That is true.

9 DR. LIPICKY: That you don't know whether  
10 people with ischemia are adversely affected because  
11 there isn't enough data. And that people with heart  
12 failure are certainly at greater risk of Torsade.

13 And you concluded all of this from the 43  
14 events that you saw?

15 ACTING CHAIRMAN CALIFF: Which is the best  
16 data base that we have access to, or that we've seen.

17 DR. LIPICKY: But it is from that 43  
18 patients that you drew those conclusions?

19 ACTING CHAIRMAN CALIFF: That is all we  
20 have. But I think denoting increased risk, and  
21 specifying who should be treated are two different  
22 things.

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1           For example, we know patients at highest  
2 risk of complications from bypass surgery are the very  
3 ones who probably should be treated. So it has to be  
4 an assessment of risk and benefit.

5           Which gets us to, I think, we have to add  
6 a new question five, which is really the key question.  
7 I think the panel has unanimously agreed that the drug  
8 is effective in preventing relapse of atrial  
9 fibrillation, and also in converting.

10           There is differences of opinion over the  
11 importance of that relative to symptoms, and there is  
12 unanimous agreement that proarrythmia is the only  
13 concern.

14           And now we have to, I think, weigh those  
15 two issues and say whether we think, on balance, this  
16 is a drug that should be -- should be approved. Is  
17 that question 8? Okay.

18           I think if the answer is no, then the rest  
19 of these questions become relatively unimportant. If  
20 the answer is yes, then I think they become very  
21 important.

22           DR. LIPICKY: Well, I guess it depends on

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1 your logic, right? It seems to me if you cannot  
2 decide what dose should be used, you can't answer the  
3 question. That certainly has to influence your answer  
4 to question 8.

5 If you can figure out what dose to use  
6 that has to influence your answer to question 8. So  
7 it isn't clear to me that although, granted, you could  
8 go to question 8 right away, and then not answer any  
9 of these other questions, it sort of is like, well I'm  
10 sure it works, therefore it should be approved, but I  
11 don't know what dose to give it in. That is not a  
12 good recommendation.

13 And similarly 6, if the notion is, we know  
14 there are bunches of things available out there, and  
15 they have no risk at all, and this has a risk, I don't  
16 see how you can answer 8 until you make the decision  
17 about what else is available in the area for  
18 treatment.

19 So you can -- I wouldn't object if you go  
20 to 8 right away. I'm just pointing out there is some  
21 reason for going this route, as opposed to jumping.

22 DR. KOWEY: I for one would like to hear

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1 the Committee talk about these questions before we get  
2 to 8. I think there is an order to this, and I kind  
3 of appreciated the order. And I think if we go to 8  
4 right now it is going to preempt a lot of good  
5 discussion we need to have.

6 So I would vote that we continue.

7 ACTING CHAIRMAN CALIFF: Is everyone else  
8 in agreement with that? I almost feel like the  
9 impeachment hearings. I guess we will call the  
10 witnesses if that is what people want to do.

11 (General laughter.)

12 ACTING CHAIRMAN CALIFF: So question 5.  
13 Peter, you wanted to talk about this?

14 DR. KOWEY: It is okay. It is not going  
15 to be comfortable, but I think we should do it. The  
16 answer to this is I think yes. I think there are  
17 other considerations -- the question has to do  
18 starting the drug during a three day hospitalization  
19 with dose adjustment to take account of renal function  
20 and observed changes in the electrocardiogram.

21 Are there considerations of patient's  
22 weight, sex, and phenotype? Phenotype I don't

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1 understand. But yes for patient weight, sex,  
2 drug/drug interaction, organ dysfunction, which should  
3 affect dosing. Yes, the answer is there certainly are  
4 major ones.

5 DR. GRINES: Yes, I agree. I think the  
6 low body weights, female gender, moderate liver  
7 dysfunction, all these drug interaction appear to be  
8 of some concern.

9 ACTING CHAIRMAN CALIFF: Bob?

10 DR. TEMPLE: Yes.

11 DR. GRABOYS: Yes, and I just want to add  
12 my continued discomfort about the heart failure in  
13 post-MI populations, where the approach used by the  
14 sponsor in Diamond was different from in the rest of  
15 their population. And I'm still stuck with that.

16 So I guess I would add that as another  
17 point, is that in patients with atrial fibrillation  
18 who are post-MI, or with heart failure, I think we  
19 have to consider, and I don't know what to do about  
20 it, but consider a slightly different dosing approach,  
21 based on the data that we have.

22 ACTING CHAIRMAN CALIFF: Tom?

1 DR. BIGGER: Yes. I think there are  
2 issues here that have to be labeled, and that is about  
3 it.

4 DR. PIÑA: Yes, but I really don't know  
5 what kind of recommendations that we should give on  
6 dosing, because as Marvin said, all we have is the  
7 dosing that were used in this regimen, and I'm not  
8 sure how to say to a clinician you need to adjust  
9 downward because of gender, or because of -- I know  
10 about renal dysfunction because that is an easy -- and  
11 I know about looking at the QT, but I don't know what  
12 advice to give, but I think yes, that it needs to be  
13 addressed.

14 DR. D'AGOSTINO: Yes.

15 DR. LINDENFELD: I think yes for some  
16 things. Drug/drug interactions, I think weight is  
17 taken into account in the creatinine clearance  
18 calculation. And the sex concerns me because that  
19 wasn't done in these protocols, and if we do it, and  
20 we adjust downward for women, are we going to have any  
21 effect at all?

22 So this is a confusing set. But I think

1 for some of the clear drug interactions yes.

2 ACTING CHAIRMAN CALIFF: I would say yes,  
3 also. Incredibly complicated, and as we will get to,  
4 maybe requiring much longer discussion in a different  
5 venue. Bob?

6 DR. TEMPLE: As various people pointed  
7 out, no adjustments were, in fact, made in the Diamond  
8 trial for any of these factors, and at least as far as  
9 drugs go, everybody was on lots of them. How does  
10 that affect you?

11 I think Joan's question is perfectly  
12 right. How would you know you had any effect if you  
13 have the dose in women, how would you know anything?  
14 So, if we discovered some major interaction that  
15 doubled everybody's blood level, okay, we could figure  
16 out how to deal with that.

17 But short of a major new discovery what is  
18 one supposed to do? Or maybe what you are saying is  
19 that when you discover something that has a major  
20 impact on area under the curve, make appropriate  
21 adjustments.

22 ACTING CHAIRMAN CALIFF: My interpretation

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1 of what people are saying is that so much data was  
2 presented today, there were some relatively specific  
3 things, like Verapamil, and then there were some  
4 general drug classes where more work needs to be done.  
5 They are the nephric patients who have not been  
6 studied.

7 DR. TEMPLE: Well, they don't recommend --  
8 I think they don't recommend the use for anybody below  
9 20 creatinine clearance, right?

10 ACTING CHAIRMAN CALIFF: But we also know  
11 that people will develop, in the course of treatment,  
12 will develop deterioration of renal function that  
13 needs to be dealt with.

14 DR. TEMPLE: So that implies to me that  
15 you think there ought to be something about continuous  
16 monitoring of renal function.

17 DR. LIPICKY: Well, are you talking about  
18 the acute phase that is the conversion phase, or are  
19 you talking about the maintenance phase, or are you  
20 talking about the in-hospital preparation for the  
21 maintenance phase, or l--

22 ACTING CHAIRMAN CALIFF: All the above.



1 I think there have to be recommendations.

2 DR. LIPICKY: Well, don't you think -- I  
3 mean, I'm just, it seems to me that those are very  
4 different situations in the acute treatment phase, you  
5 know, Dr. Atkinson suggested that it could be that a  
6 lot of people convert at lower blood levels than it  
7 looks like on the slide, and you could certainly do  
8 some titration if you are convinced that the stuff  
9 works, even in the absence of an empirical data base  
10 that says that that is true for the preparation to go  
11 out-patient, right? You have to get on some stable  
12 dose that gives you a QT that is tolerable.

13 So you could shoot for a low dose and wait  
14 for a recurrence. And I mean, recurrence of AF is no  
15 big deal, you just get converted again, right? And if  
16 that isn't the right thing, then you up the dose,  
17 again, in the hospital.

18 And then maybe you would finally get the,  
19 so I'm not sure I know what of those three different  
20 potential ways you can solve all of these problems,  
21 for each of the three phases, and I don't think you  
22 should lump them?

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1 DR. KONSTAM: I think the problem that I  
2 have with the last approach that you are mentioning is  
3 that we don't have any data about it. And we don't  
4 have any efficacy data --

5 DR. LIPICKY: Sure you do. What do you  
6 mean you don't have any data?

7 DR. KONSTAM: Well, to tell us what would  
8 happen, and how, and what rate of success --

9 DR. LIPICKY: You don't know what would  
10 happen if you went from a low dose to a high dose?  
11 How can you say that? You certainly have the data  
12 that tell you that at a dose of somewhere around the  
13 lowest dose something might happen, but it isn't  
14 spectacular.

15 And in between there and the highest dose  
16 there is a relatively big change. You know that. Can  
17 you seriously doubt that that would happen if you did  
18 that in practice?

19 DR. TEMPLE: You sort of do have data, you  
20 know what the recurrence rate was on, say, 250. So if  
21 somebody thought it was a good idea to say your  
22 initial crack at this ought to be limited to 250,

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1 because you think that would be safer, you know that  
2 the recurrence, you know, the time of recurrence will  
3 be thus and such, better than placebo, not as good as  
4 500.

5 And there is no particular reason to think  
6 that if you then went on to 500 they would be any  
7 different from patients entering on 500. So you sort  
8 of know, even though it wasn't done that way.

9 DR. LIPICKY: There is no more reason here  
10 to hit people with the biggest gun than there is when  
11 you start an anti-hypertensive drug. Now, some people  
12 would say you should, you know? But you certainly can  
13 start with the small dose and up it.

14 I guess I look around the panel I don't  
15 hear anybody basically disagreeing with you that this  
16 is any different than hypertensive trials where you  
17 start at a dose and may work your way down.

18 DR. KONSTAM: I think you are convincing  
19 me, so -- but the only difference is that the efficacy  
20 here is not truly by variate. It is really, we are  
21 talking about efficacy in terms of the endpoints that  
22 we see, in terms of statistical likelihood of staying

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1 in sinus rhythm.

2 DR. LIPICKY: No, you only had three arms,  
3 so you can only get three bars, and that looks like it  
4 is not continuous. But the QT versus plasma  
5 concentration looks continuous, right? And it doesn't  
6 -- I mean, we are not talking bivariate, trivariate,  
7 or anything else.

8 All you have to do is assume that there is  
9 a continuous relationship between plasma concentration  
10 in any of these things. If you really think it is  
11 some big mystery, like somehow or another you will  
12 fall into that box, and if you don't fall into that  
13 box nothing happens, then you have to think of it in  
14 some discontinuous way.

15 But I see no reason to do that here.

16 ACTING CHAIRMAN CALIFF: I don't see  
17 anybody really disagreeing with that.

18 DR. LINDENFELD: Well, let me just ask.  
19 If you start people with a normal creatinine clearance  
20 on a lower dose, you are not going to expect to get  
21 the same efficacy that --

22 DR. LIPICKY: You would apply the same

1 rules. You know, if you were going to start, if you  
2 thought 125 micrograms was the one that was a  
3 reasonable starting dose, you would 125 microgram that  
4 person according to the same rules, and then you go up  
5 to the 250 according to the same rules. And then you  
6 would go up to 500 according to the same rules.

7 ACTING CHAIRMAN CALIFF: You are saying we  
8 have definable relationships, and you might get to the  
9 same point by several different approaches. And I  
10 think we are saying, based on the data we've seen, we  
11 can't say which approach is best.

12 DR. LIPICKY: The only decision you have  
13 to make, I think -- I'm not supposed to talk you into  
14 anything, right? I mean, that was the wrong thing to  
15 say, Marvin. Is that the stuff works, and that there  
16 is a way in which it can be administered that is  
17 consistent with how you understand it works.

18 And then you have to evaluate, as best as  
19 you can, the risk benefit. And the only critical  
20 thing is whether you think 125 is better than placebo,  
21 okay, because that fixes one end of the extreme that  
22 you are working with.

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1 DR. KONSTAM: I see this as applicable to  
2 the chronic maintenance phase. I don't think it is at  
3 all applicable in the acute phase, because I don't see  
4 dosing up over a week.

5 DR. LIPICKY: -- in a hospital, and there  
6 are 47 incidences of documented Torsade, three deaths,  
7 8,000 patients, 47 documented Torsades, and three  
8 deaths.

9 I mean, what are the odds of somebody  
10 dying of Torsade? I thought Torsade was lethal,  
11 right? You got Torsade you were dead. No, they had  
12 47 and only three died. That surprises me. Isn't  
13 that what the data is?

14 DR. KONSTAM: They have 47 known Torsade.

15 DR. LIPICKY: Torsade, and three deaths.

16 ACTING CHAIRMAN CALIFF: Well, let's move  
17 on to B and C, which I think can be lumped together.  
18 B is, if people do it perfectly, as in the trial, do  
19 you think that patient experience will mirror what  
20 happened in the trials, and C is in the real world do  
21 you think things will be different?

22 DR. KOWEY: It appears, in the clinical

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1 trials that if you think of the first, of the  
2 hospitalization period being three days, although it  
3 doesn't have to be three days, that three quarters of  
4 the events were in the first -- in that  
5 hospitalization period.

6 So a quarter of the events should occur  
7 out of a hospital. However, I think the only way to  
8 get any kind of an estimate of what kind of mayhem  
9 could be created with this drug is to look and see  
10 what happens when the drug is overdosed.

11 And -- because that is the fear we have,  
12 is that people will use an inappropriate dose, in an  
13 inappropriate patient. And when you do that, chances  
14 of Torsade go up about five fold according to what  
15 happened in the 740 milligram, or microgram  
16 experience.

17 So if you guys want some kind of an idea  
18 of, is the world going to come to an end? Well, I  
19 think that is a lot of Torsade. And I think that is  
20 five-fold differences is pretty dramatic.

21 So I think there is opportunity here for  
22 a lot of havoc if people don't pay attention to the

1 way they should dose the drug. If that is what the  
2 intention of the C question is, that is what I think  
3 would happen.

4 DR. TEMPLE: It is to get at all of those.  
5 If they don't use hospitalization, if they don't get  
6 rid of people whose QT gets too long and, of course as  
7 you said, if they use a bigger dose, you could  
8 probably think of more things, too.

9 DR. GRINES: I think it is difficult to  
10 answer B, but question 5C, you know, there is no way  
11 that the clinician is going to monitor the patients as  
12 closely as what the trial did.

13 DR. TEMPLE: Do you mean in-hospital or  
14 after?

15 DR. GRINES: Both, absolutely both. They  
16 are not going to measure ten to fifteen beats to  
17 average the QT, they are not going to give frequent  
18 ECGs. You know, I don't know anybody who sees a  
19 patient back as frequently as any of these trials  
20 request.

21 And, furthermore, you see a lot of  
22 patients who revert back to atrial fibrillation whose



1 doctors keep them on Quinidine for 15 years. You  
2 know, they don't even both to ever discontinue the  
3 drug.

4 So I think it is likely that in the real  
5 world there is going to be a much higher side effect  
6 profile. So the answer to 5C would be, increased  
7 incidence. 5B, if everything was done perfectly I  
8 suppose it would be a pretty low incidence, similar to  
9 the trials.

10 DR. LIPICKY: Do either you or Peter,  
11 since you were answering this, think that this is  
12 likely to wreak more havoc than Quinidine does?

13 DR. KOWEY: No, I wouldn't say that.

14 DR. GRINES: No.

15 DR. LIPICKY: Okay, so that is fine.

16 DR. KOWEY: I think that is coming up.

17 DR. BIGGER: I took some encouragement  
18 from the setting in which the Diamond studies were  
19 done, where a large fraction of the population was  
20 treated, and is mentioned, a lot of it was FP/IM and  
21 not cardiology. And the results, adverse effects,  
22 were pretty low.

1 DR. GRINES: Yes, but they monitored them  
2 very closely, and 50 percent of them decreased or  
3 stopped the drug. So I don't think in the real world  
4 that is going to happen.

5 DR. GRABOYS: I think it is going to  
6 depend on what the substrate is, and it is going to  
7 depend on what the clinical profile of the patient is.  
8 I think Peter used the word mayhem, and I think that  
9 is an appropriate word, and that is going to describe  
10 what is going to happen if this sloppy dosing, which  
11 I think there is every indication there probably will  
12 be, and particularly if there is a vulnerable  
13 substrate, if you get a cardiomyopathic, or you get a  
14 patient, most of these patients in AF, with structural  
15 heart disease in a polypharmacy, anyway.

16 DR. KONSTAM: You know I don't think we  
17 know what the incidence of at a hospital lethal  
18 arrhythmia is going to be. I think that the we don't  
19 know as much about it as I think we think at first  
20 blush.

21 I think if you look at the Diamond trials  
22 you are dealing with one year mortalities in the 20

1 percent range, and that is against the defined Torsade  
2 incidents during observation, or to a degree of  
3 confidence we know that the Torsade incidence in the  
4 .8 percent range.

5 And I don't even know what the time frame  
6 is that that represents, exactly. So we don't really  
7 know to what extent Torsade or lethal Torsade is  
8 hiding within the Diamond population.

9 So, you know, in terms of what is the  
10 percent, you really have to look at, for example, the  
11 supraventricular arrhythmia data set, you know, again  
12 where you have 12 deaths out of 1,300 patients, about  
13 half as many in the placebo, so maybe it is .5 percent  
14 lethal arrhythmias occurring, maybe it is, maybe it  
15 isn't, because the number of events is pretty small.

16 So we don't really know. I mean, it is --  
17 we know it is finite, I would not believe that it is  
18 zero, it is probably -- no reason to believe it is any  
19 worse than Quinidine, my guess is it is better than  
20 Quinidine.

21 But the good news is, here, we know  
22 tremendously more about it, and what we might, and an

1 approach to dealing with it that we don't have with  
2 other antiarrhythmics that we have.

3 So I don't know if that answers B or C at  
4 all, but that is my feeling about the whole subject.

5 ACTING CHAIRMAN CALIFF: Tom?

6 DR. BIGGER: -- real world setting in  
7 which they did this, they didn't encounter a lot of  
8 problems. I think actually doctors, when they read  
9 this label, the way I envision it is going to look,  
10 are going to go low on the doses, anyway.

11 ACTING CHAIRMAN CALIFF: Ileana?

12 DR. PIÑA: I agree with Tom. I think that  
13 if used properly the out of hospital malignant  
14 arrhythmias may be small. What would happen in  
15 prescribing is less careful, I really don't know, but  
16 I suspect that there would be more proarrhythmic events  
17 if people get careless with higher doses.

18 DR. D'AGOSTINO: I think the 5B, the 5C,  
19 could potentially be quite high, and this is what I  
20 was concerned about in terms of the second study is,  
21 were they going to go higher and higher to get the  
22 effect.

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1 I think the way we are talking about start  
2 off with a low dose and build up, if it is done like  
3 that, and held, again 5B will be low, and 5C has  
4 potential of problems, but there is nothing more that  
5 we can say then I think that we could possibly have  
6 serious problems.

7 ACTING CHAIRMAN CALIFF: Joan?

8 DR. LINDENFELD: I agree, I think B will  
9 be low, although I don't think it will be as low as in  
10 this study, because I think there is a difference,  
11 from regular clinical practice in having a coordinator  
12 making sure that these things are done in each visit.

13 I think C will be higher. The one thing  
14 that concerns me here is that we don't see with  
15 Quinidine, is the problem with renal failure, the  
16 patient with severe heart failure who comes in with a  
17 doubling of their BUN and creatinine, which will  
18 affect this drug a lot more than Quinidine.

19 ACTING CHAIRMAN CALIFF: Well, I would say  
20 to B that I would guess more like -- there will be  
21 more like the clinical trials, since the trials tended  
22 to be more real world than other clinical trial

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1 packages that we have seen, which I think is a very  
2 important part of the development program. I agree  
3 with Tom.

4 And C could be a disaster if not handled  
5 very well. Just the incredible use of Quinidine that  
6 we saw this morning probably is a tremendous disaster,  
7 I would say.

8 So it is a concern. And I guess the  
9 message we are giving is that if this was allowed out,  
10 it would need to have a very careful program of some  
11 kind.

12 We move on to 6, which is really oriented,  
13 Peter, as you see, to the question of how do we weigh  
14 this against other agents which are currently in use.

15 DR. LIPICKY: Since time is flying, I will  
16 just -- this could have been a very interesting  
17 discussion, but your answer to these questions could  
18 be as simple as, how the hell do we know, they didn't  
19 do anything head to head.

20 It could be a very interesting set of  
21 discussions that would rely on a bunch of stuff. So  
22 use your head how you are going to --

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1 DR. KOWEY: It is a good thing to use.  
2 Actually, I was going to answer all three at once,  
3 because I think they are all part of the same --  
4 rather than trying to do each one separately, because  
5 I do think your -- I think you are probably right,  
6 although there is a little bit more you can add.

7 If you look at the Sotalol comparator in  
8 the 345 trial, it looked like the drug was -- Sotalol  
9 was in the middle of the pack in terms of those  
10 Kaplan-Meier curves that we saw.

11 But that is not really a dose of Sotalol  
12 that we use in real life for atrial fibrillation. I  
13 mean, we usually use higher doses than that, and that  
14 is probably why they didn't see any Torsade in the  
15 Sotalol arm.

16 So the answer to the question, I would  
17 like to be able to see comparator data, I thought I  
18 was, when I first started reading 345 and got a little  
19 excited and thought we would actually see some data.  
20 But I don't think they include anything from that.

21 I do think that looking at its non-  
22 proarrythmic side effect profile that, clearly,

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1 without a comparator trial, I don't need one, thank  
2 you.

3 But it clearly is better tolerated than  
4 most 1A drugs, and probably better tolerated than  
5 Amiodarone over the long term, because we just simply  
6 didn't see any, or very much in the way, we already  
7 admitted that, side effects.

8 So I think C is probably -- it is  
9 superior. A and B I think I agree with you Ray, I'm  
10 not really getting the feeling that we can answer that  
11 question adequately.

12 ACTING CHAIRMAN CALIFF: Cindy?

13 DR. GRINES: I think I agree, in general.  
14 I just wanted to ask the sponsor, I think it was in  
15 the FDA review they talked about small trial compared  
16 to Quinidine, and they commented on more  
17 discontinuation due to some test results in the drug  
18 arm compared to Quinidine. And the number that I  
19 wrote down here is 23 versus 12 percent.

20 But I don't know which trial, specifically  
21 it was.

22 DR. RYDER: I believe that was a small PAF



1 study comparing Dofetilide. Do you recall the dose?  
2 250 micrograms to Quinidine, and the dose of Quinidine  
3 I don't recall.

4 DR. GRINES: But what were the test  
5 results that resulted in 23 percent of patients having  
6 the drug discontinued?

7 DR. RYDER: We will have to check that.

8 DR. GRINES: Okay.

9 ACTING CHAIRMAN CALIFF: Tom?

10 DR. GRABOYS: I can't answer A, probably  
11 not to B, and yes on C.

12 ACTING CHAIRMAN CALIFF: Marvin?

13 DR. KONSTAM: I agree that I can't answer  
14 A. I think with regard to B, I can't really answer  
15 it, except to say I do think that we have an approach  
16 to dosing of this drug that I believe is going to --  
17 if adhere to rigorously, will be less proarrythmic  
18 than what we have out there.

19 So I think given -- in that context I  
20 think it has the potential for being less  
21 proarrythmic.

22 And I think that as others have said, that

1 non-proarrhythmic side effects are considerably less  
2 than the other drugs that we have available.

3 ACTING CHAIRMAN CALIFF: Tom?

4 DR. BIGGER: I took this on by just  
5 thinking about the literature, and I think for 6A that  
6 it doesn't seem to be markedly more effective or less  
7 than available therapy, that is pretty clear to me  
8 that it was true.

9 I don't think it is markedly more  
10 proarrhythmic than drugs we have available to us, and  
11 it has some other toxicity seems to be lower, aside  
12 from the proarrhythmic type.

13 And I didn't think the proarrhythmic side  
14 effects were more prominent than available therapy.  
15 That is not giving a great recommendation, however.

16 ACTING CHAIRMAN CALIFF: Ileana?

17 DR. PIÑA: I personally can't answer 6A or  
18 B definitively. I agree that the side effect profile  
19 here is, at least in my experience, much more  
20 acceptable than what we have right now with the drugs  
21 we have.

22 DR. D'AGOSTINO: No to A and B and C I

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1 don't know.

2 DR. LINDENFELD: I think A and B are about  
3 the same, and C is better tolerated. I think A and B  
4 is about the same as what we have now, probably.

5 DR. TEMPLE: Rob, can I ask something?  
6 Every large trial I know about involving Quinidine  
7 showed that it was worse than -- that it was highly  
8 proarrythmic, lethal, and all that.

9 Here you have the Diamond trials and they  
10 show nothing like that, nobody is impressed by that?

11 DR. GRINES: Yes. I would like to comment  
12 on that. You know, a lot of these Quinidine trials  
13 were done back in the era when nobody recognized  
14 proarrythmic effect, and they weren't monitoring QT  
15 intervals.

16 I think this is very different, these  
17 patients were very highly selected, they had the drugs  
18 discontinued, or decreased for the, you know, numerous  
19 reasons.

20 DR. TEMPLE: Absolutely. I meant when  
21 used as it was used, all those other drugs, nobody  
22 knows how to use them, or at least not that anybody

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1 can say.

2 DR. GRINES: Right.

3 DR. GRINES: Well, I would hope now that  
4 if I had a patient with Quinidine and they had a long  
5 QT interval I would do something, or if they had a  
6 proarrythmic event I would stop it.

7 DR. TEMPLE: It is not that that couldn't  
8 be, but the only attempts to pool available data with  
9 Quinidine have shown disastrous outcomes.

10 ACTING CHAIRMAN CALIFF: Well, my answer  
11 was going to be related to that, which is markedly  
12 more effective. I wish we had a head to head trial,  
13 I can't say, does it appear to be more proarrythmic?  
14 It looks markedly less proarrythmic than Quinidine the  
15 way it was used.

16 But I think we are caught between not  
17 knowing whether this is intrinsically badness of  
18 Quinidine, or just absence of knowledge about  
19 Quinidine.

20 So if the question was, is a less  
21 proarrythmic than Quinidine used in the absence of  
22 current knowledge, the answer is clearly yes, in my

1 opinion. Could the Quinidine problem be corrected?  
2 We just don't know, because it hasn't been looked at,  
3 but we would like to know.

4 And I think everyone has answered C, that  
5 looks like less side effects.

6 So we come to 7 and 8. We could go step  
7 wise, Ray, or could we answer 7 and 8 together?

8 DR. LIPICKY: Sure. You can answer them  
9 together.

10 ACTING CHAIRMAN CALIFF: Because I think  
11 we've agreed on the efficacy side for both 7 and 8,  
12 that the evidence is there.

13 Now we come down to the balance. Should  
14 it be approved for use in all patients, or for use  
15 only in some subset of patients? If so, should it be  
16 approved.

17 DR. LIPICKY: 7 and 8 are, do you want to  
18 approve conversion, and 8 is do you want to approve  
19 prolonging the time to recurrence. And you can put  
20 both of them together and get a simple yes or no  
21 answer, if you wish. Is the whole package approvable  
22 or --

1 DR. TEMPLE: But if you didn't want to  
2 approve maintenance you would never approve  
3 conversion.

4 DR. LIPICKY: No, no, no. Ibutilide was  
5 approved for conversion and it had no maintenance  
6 regimen at all. It doesn't have to be.

7 ACTING CHAIRMAN CALIFF: Let's try them  
8 both, and if it doesn't work we will go back.

9 DR. KOWEY: I would vote yes for both.

10 ACTING CHAIRMAN CALIFF: Cindy?

11 DR. GRINES: I think I'm going to vote no.

12 ACTING CHAIRMAN CALIFF: Do you want to  
13 elaborate, since --

14 DR. GRINES: Well, I agree that it is  
15 efficacious, but I'm just concerned that we don't --  
16 I mean, if you read into 8A, and some of the  
17 qualifying statements I would make if I did recommend  
18 approval, I can't even qualify it, because I haven't  
19 seen the breakdown of these highly symptomatic, or  
20 various subsets of patients.

21 And so rather than, you know, dig myself  
22 in a hole I would have to say no.

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1 ACTING CHAIRMAN CALIFF: Tom?

2 DR. GRABOYS: No.

3 ACTING CHAIRMAN CALIFF: Marvin?

4 DR. KONSTAM: I am going to vote yes. You  
5 know, but we are being asked -- we are voting on both  
6 at the same time because I think we are also being  
7 asked, in all patients, or with subset of patients.  
8 And I wouldn't approve it on all patients in --

9 ACTING CHAIRMAN CALIFF: No, that is the  
10 next question.

11 DR. KOWEY: Let me just make sure that I  
12 stipulate that as well. The question is, is it  
13 approvable? But we haven't talked about what  
14 populations, or what labeling, or anything like that  
15 yet?

16 DR. TEMPLE: Yes means under some  
17 conditions for some population, no means under no  
18 conditions for any population, right?

19 DR. KONSTAM: Yes.

20 ACTING CHAIRMAN CALIFF: Tom?

21 DR. BIGGER: Yes, I would think it is  
22 approvable.

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1 DR. PIÑA: Yes.

2 DR. D'AGOSTINO: Yes.

3 DR. LINDENFELD: Yes.

4 ACTING CHAIRMAN CALIFF: I would also vote  
5 yes on that question. So we now come to the issue of,  
6 should it be approved for use in all patients, or for  
7 use only in some subset. And for those who voted no,  
8 it is not that you are out of the vote here, I think.

9 I think we are all still interested in  
10 your opinion on this.

11 DR. KOWEY: This is, obviously, the most  
12 important part of this discussion, from my point of  
13 view, because it now gets into the question of how  
14 this drug is -- this is the beginning of the  
15 discussion about labeling.

16 My own opinion about this is that I don't  
17 -- even though the FDA reviewers have felt fairly  
18 strongly about this, and have actually put forward, I  
19 think, a fairly cogent argument that it only should be  
20 in patients with class 2/3 neocard association class,  
21 for example, I don't agree with that.

22 I think the data really do extend across

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1 most functional groups, or all the functional groups  
2 that were examined. I think it would be inconsistent,  
3 at this point, to limit it, especially if one looks at  
4 risk benefit.

5 And we have already said that we think  
6 there is more risk in those patients that have LV  
7 disfunction. So I would, as I -- I guess that is a  
8 long winded I would vote that it should be approved,  
9 potentially, for patients with and without structural  
10 heart disease, pending further discussion about other  
11 labeling issues.

12 DR. KONSTAM: Goodbye, Dr. Califf. I've  
13 been asked to take over the chair.

14 Can I just ask Bob and Ray, the people who  
15 voted no should -- you want their opinion about what  
16 subsets they would approve it? I'm not sure what the  
17 logic about it --

18 DR. LIPICKY: Sure. It really -- they  
19 voted no because they were worried about something,  
20 and they were probably worried about something for  
21 some particular reason, and that would contribute to  
22 this.

1 DR. KONSTAM: Right, but I assume that if  
2 they voted no they are saying there is no subset of  
3 patients in which they would approve it?

4 DR. LIPICKY: Well, that is --

5 DR. KONSTAM: Is that not true?

6 DR. GRINES: Well, I guess --

7 DR. LIPICKY: Under any condition. There  
8 was no subset under any condition. There may be some  
9 subset under some condition.

10 DR. KONSTAM: Do they have to go back and  
11 change their other vote to yes? If we could get them  
12 to do that?

13 DR. LIPICKY: Well, that is how it happens  
14 sometimes.

15 DR. KONSTAM: Cindy is there some  
16 population that you are thinking about --

17 DR. GRINES: Well, I guess so, we've  
18 tossed around a lot the symptomatic patient, and I  
19 agree that there are patients who are very  
20 symptomatic, low cardiac outputs, and need the atrial  
21 kick, etcetera, that could potentially benefit from a  
22 symptomatic standpoint.

1                   And I guess the reason I voted no was due  
2                   to my concern about proarrythmic effect, and also the  
3                   fact that we weren't able to see the data on that  
4                   population.

5                   And so it is very difficult for me to even  
6                   suggest a population without having any data to  
7                   support that.

8                   DR. KONSTAM:        So there isn't any  
9                   population that you think is close?

10                  DR. GRINES:  No, I think theoretically,  
11                  theoretically there are a number of patients who may  
12                  benefit.  I just don't think that the data that has  
13                  been provided allow me to vote in that direction.

14                  DR. KONSTAM:  Bob?

15                  DR. GRABOYS:  I just don't trust the  
16                  physician population out there.  I think that is my  
17                  concern.  And that the large fraction of folks with  
18                  atrial fibrillation, AF is a benign problem, meaning  
19                  you put a patient on anticoagulants, you do -- you  
20                  effect rate control, it is a benign situation.

21                  But I can see that benign situation all of  
22                  a sudden turning into a malignant situation because of

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1 a drug that has significant potential for proarrythmia  
2 or Torsade.

3 DR. KONSTAM: Bob, did you have a comment?

4 DR. TEMPLE: Yes, I just wanted to say,  
5 there can be a number of reasons that you might want  
6 to limit a population, and at least in some cases we  
7 haven't always thought you needed data.

8 For example, if on safety grounds you want  
9 to reserve a drug only for people who were intolerant  
10 of another drug, we've not insisted that you literally  
11 prove that there are people who are intolerant of the  
12 other drug and then study them, because it was  
13 perceived as somewhat obvious that as long as there  
14 are people who are intolerant of another drug they are  
15 probably not intolerant to this one, too.

16 You could argue those points, but one  
17 could do it. So if someone thought here that these  
18 risks are acceptable only in people who are  
19 significantly disabled by their disease, you could  
20 recommend that to us, even though you don't actually  
21 have a population of people who were disabled by their  
22 disease on the grounds that it is obvious if they are

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1 disabled by being in fibrillation, then they have more  
2 to gain from that.

3 So you could do that even though we don't  
4 actually literally have that population. It would be  
5 not so easy to find that population, unless they are  
6 a large fraction of it. But we could listen to that  
7 recommendation, even though you don't actually have  
8 data, if on safety grounds you thought that was a  
9 reasonable limitation. Now, you might not think that,  
10 but you could.

11 DR. KONSTAM: Tom?

12 DR. BIGGER: Well, I'm looking at this  
13 large data base which is more than we usually see, and  
14 I would be willing to approve it for symptomatic  
15 patients who are, in the judgement of the physician,  
16 the benefits outweigh the risks.

17 DR. KONSTAM: Ileana?

18 DR. PIÑA: I would agree with that. I  
19 think symptomatic patients, where the benefits of  
20 conversion to normal sinus rhythm is desired, and I  
21 would also look at the Diamond data. I mean, it is a  
22 very large body of data of patients with ventricular

1 dysfunction. And I think that is very powerful data.

2 DR. KONSTAM: Ralph?

3 DR. D'AGOSTINO: I think it should be  
4 approved for all patients. Obviously you have  
5 concerns about how you would treat individual subsets,  
6 and so forth, but I think the approval should be for  
7 all patients, which are chronic AF.

8 DR. KONSTAM: Joan?

9 DR. LINDENFELD: I like the statement  
10 symptomatic patients, I think that -- at least then  
11 hopefully we are subjecting patients who have a  
12 greater potential benefit to the risk of the drug.

13 DR. KONSTAM: I'm going to come down  
14 fairly close to what Tom Bigger said. I would not  
15 approve it in all patients. I would approve it for  
16 patients who were significantly symptomatic, and/or  
17 limited by atrial fibrillation, and exactly the words  
18 that he used, in whom the physician's judgement is  
19 that the risk benefit ratio warrants its use, even  
20 considering the risk of Torsade.

21 Bob?

22 DR. TEMPLE: Those are somewhat different

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1 answers that people have given. I don't know if you  
2 want to try to get together and resolve them, or just  
3 leave us with that.

4 But everyone agreed -- almost everyone  
5 agreed it should be for people who are symptomatic.  
6 But symptomatic could mean an occasional palpitation,  
7 symptomatic could also mean, I think about it all the  
8 time, my life is poisoned.

9 Any other comments from -- or we can hear  
10 a range of views, and we've heard that. I just wonder  
11 if anybody who said symptomatic wants to respond to  
12 the more stringent symptomatic description than Marv  
13 just gave.

14 DR. KOWEY: I would like not to do that.  
15 I would actively like not to do that, because I think  
16 we are going over physician judgement, and really  
17 something Tom said a little bit earlier about how  
18 devastating this disease can be to people who may not  
19 necessarily have provable hemodynamic compromise, for  
20 example, but whose lives really are sometimes ruined  
21 by this arrhythmia.

22 And it really is necessary not just to

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1 counsel them, but also to get them out of it.

2 DR. KONSTAM: But, Peter, why is that  
3 different from what Bob just said?

4 DR. KOWEY: No, he said significant  
5 symptoms and I don't want to get into a discussion.  
6 I personally don't want to get into a discussion of  
7 what is significance. I don't think that is something  
8 that we should do.

9 I think we should just tell the  
10 physicians, if the patient is symptomatic, and in your  
11 judgment that patient will benefit from being in sinus  
12 rhythm, and the benefit outweighs the risk, then that  
13 is when the patient should get the drug.

14 That is what I think.

15 DR. TEMPLE: Tom, is that what you meant?

16 DR. KONSTAM: I'm not sure we disagree.  
17 I mean, Peter, what you just said is there are some  
18 patients -- I think you said something like there are  
19 some patients who are going to be devastated by having  
20 atrial fibrillation. And something like that.

21 And why is that different from saying, I  
22 mean --

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1 DR. KOWEY: Because I've been at other  
2 meetings like this where we've gotten into discussions  
3 of trying to define what we mean by significant  
4 symptoms. And it really becomes a trap, in some  
5 extent, that you can't -- it is really very hard to do  
6 that.

7 DR. LIPICKY: You would get into which  
8 symptom is significant, how you can tell that it is  
9 significant, and what kind of documentation --

10 DR. TEMPLE: You don't have to. You don't  
11 have to. There is more than one way to do this. But  
12 say symptomatic is one thing, to say symptomatic in a  
13 way that really severely affects the patient's  
14 existence is another. I mean, there is a range of  
15 things one could say.

16 DR. LIPICKY: Yes, but what is the  
17 difference between those words? That is what Peter  
18 was saying.

19 DR. TEMPLE: Symptomatic mean I'm aware of  
20 my fibrillation because I have an occasional  
21 palpitation.

22 DR. LIPICKY: Yes. And the others?

1 DR. TEMPLE: Severely symptomatic is I  
2 think about it all the time, I can't exercise worth a  
3 damn.

4 DR. LIPICKY: But that doesn't  
5 differentiate it for me, okay? I mean, the same  
6 patient you described I think would be, unless there  
7 was some operative definition of what severe meant.

8 DR. TEMPLE: I'm just trying to find out  
9 what message the committee would like us to --

10 DR. LIPICKY: Peter said he didn't want to  
11 do that.

12 DR. TEMPLE: There have been several  
13 different things, they are not identical.

14 DR. LIPICKY: Well, I haven't heard  
15 another suggestion yet.

16 DR. GRINES: Lifestyle limiting.

17 DR. KONSTAM: What about the concept that  
18 Tom said of wording with regard in whom is the  
19 physician's judgement that the risk, that the benefit  
20 outweighs the risk, or the risk of Torsade.

21 DR. TEMPLE: We have certainly used  
22 language like that, that is another version of how to

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1 do that.

2 DR. KONSTAM: The problem with that is we  
3 don't know exactly what the risk of Torsade is. Maybe  
4 we do.

5 DR. BIGGER: Well, they are going to put  
6 it in.

7 DR. TEMPLE: Just to further check on the  
8 reasoning. My assumption is that the people who are  
9 comfortable with this are comfortable, at least  
10 partly, because the Diamond data is reassuring.

11 Is that part of everybody's -- the Diamond  
12 study data is moderately reassuring on these  
13 questions, and that is why people who are comfortable  
14 with this are comfortable with this.

15 DR. BIGGER: Yes, that is true, but if you  
16 -- let's just stop and think, you know, there is a  
17 bunch of risks listed up there, and there is all this  
18 stuff about the drug interactions, and unknowns in  
19 this region, and Torsade is a major issue here, so I  
20 will be thinking like, is the benefit of giving it for  
21 afib, that way the risk of Torsade, because that is  
22 the only risk we really --

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1 DR. TEMPLE: I understood that. For  
2 example, Peter, who didn't want to be too precise, and  
3 you don't want to be too precise about what the risks  
4 should be, I'm asking whether that is because you take  
5 some assurance from the Diamond data that the risk  
6 isn't awful?

7 I'm just trying to check the reasoning.  
8 Okay.

9 DR. KONSTAM: Okay. Maybe we can go on to  
10 8B. What sort of program, if any, should be  
11 instituted to determine what fraction of patients  
12 receiving Dofetilide in accordance with the  
13 recommended dose finding scheme should form mechanisms  
14 perhaps similar in spirit to the no blood/no drug  
15 scheme used with clozapine be implemented to reduce  
16 the likelihood of non-recommended prescribing and  
17 dispensing practice.

18 Peter?

19 DR. KOWEY: I like the idea of having some  
20 mechanism to ensure this. I think Bob already said  
21 that there are lots of different ways to do that. I  
22 kind of trust you guys -- yes, I mean, it really is

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1 breaking new ground, and I honestly can't say that I  
2 understand how easy or how difficult it would be to  
3 implement those things.

4 I don't know, I think what you want to  
5 hear from us, should you? The answer is yes, I think  
6 you should. And the thing that really makes me very  
7 concerned about this is the creatinine clearance.

8 I think that issue, more than anything  
9 else, stands out in my mind as a stumbling block to  
10 adequate use of this drug, because it is such a key  
11 element.

12 It is foreign to doctors, doctors don't  
13 know how to do it, they don't do it, they don't think  
14 about it, they always look at the creatinine and they  
15 make assumptions about the creatinine clearance serum.

16 And you guys are saying something that  
17 isn't completely and utterly different. And I think  
18 the other thing that is different is the way the  
19 dosing is going to go on in the initial phases. This  
20 requires a very intense educational effort, which I'm  
21 sure that this company is going to undertake.

22 I just want to make sure that everybody

1 understands how important that is, that it be done at  
2 a very high level, and very thoroughly. I'm very  
3 concerned about it.

4 DR. LIPICKY: But, Peter, so that I  
5 understand what your recommendation is, or why it is,  
6 should we also do that for Quinidine?

7 DR. KOWEY: If I had my druthers? Yes.  
8 I think we should educate doctors about how to use  
9 Quinidine.

10 DR. LIPICKY: Right. But I guess I want  
11 to be sure I -- you know, we do require studies like  
12 were performed, okay? But it almost seems like you  
13 are better not doing those studies, because then you  
14 don't have these horrendous requirements imposed upon  
15 you.

16 And I would like some reaction to that.

17 DR. KOWEY: I don't think that is entirely  
18 fair. I think that when I give a talk to a medical  
19 audience about atrial fibrillation, or when I do in  
20 the future, and this subject comes up of how to dose  
21 Dofetilide, it certainly is not going to be without  
22 some mention of how you dose Quinidine or

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1       procainamide, or disopyramide.

2                   I think something Tom said earlier about  
3       don't underestimate how naive doctors are to drug  
4       dosing, you can't underestimate their naivete. And  
5       for that reason -- I'm not holding these guys to the  
6       fire any more than I am anybody else, they just happen  
7       to be sitting here today.

8                   DR. LIPICKY: Right. But I guess I'm just  
9       trying to differentiate between what the impetus is.  
10       There is clearly more information here with respect to  
11       what you ought to do.

12                   And the question is, why does lack of  
13       information make one not want to monitor other drugs  
14       too?

15                   DR. KOWEY: I didn't say that, I didn't  
16       say that I didn't want to monitor other -- of course  
17       I want to monitor other drugs. But these guys are  
18       coming up with a specific way of doing it that is  
19       novel to physicians. Physicians don't use creatinine  
20       clearances, is the point that I was making.

21                   And so for that reason, talking about this  
22       particular drug, and this particular way of dosing,

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1 they have to make sure that that is done in a way that  
2 physicians will understand.

3 DR. LIPICKY: Because their data convinces  
4 you that that is what should be done?

5 DR. KOWEY: Oh, they convinced me, yes.

6 DR. LIPICKY: Yes. Because you saw what  
7 happens if they don't do that?

8 DR. KOWEY: Yes.

9 DR. LIPICKY: And that was in the one 750  
10 milligram --

11 DR. KOWEY: I think Craig Brater showed me  
12 enough data to make people believe that if you don't  
13 dose the drug properly, and you don't pay attention to  
14 the creatinine, you don't know what the creatinine  
15 clearance is, or you overestimate the creatinine  
16 clearance, that you will drive the QT interval to  
17 ranges where you clearly will have a higher Torsade  
18 risk.

19 So I don't have any problem believing  
20 that, that is easy.

21 DR. LIPICKY: Okay, fine, thank you.

22 DR. KONSTAM: You know, Ray, I think this



1 is interesting --

2 DR. LIPICKY: I believe him.

3 DR. KONSTAM: I just was going to say --  
4 I think is the issue here that -- or maybe this is a  
5 corollary to what you are saying is that some people  
6 around the table may believe that we are sort of in  
7 better shape here than we are with Quinidine because  
8 we have a lot more data here, and we actually have an  
9 approach. And that might be a good thing, and might,  
10 even under those conditions some of us, I think,  
11 believe that is less proarrythmic than Quinidine.

12 And given that I guess it is worth  
13 considering what impact whatever we say in answer to  
14 this question is going to have on the relative use of  
15 this agent, versus the use of Quinidine, which we may  
16 think is less safe.

17 So I guess that is sort of the issue.

18 DR. TEMPLE: Yes, I mean, there is a sort  
19 of warrant here, that if you use it the way we tell  
20 you, things will work out pretty well, we have all  
21 this data.

22 But if nothing is done to make sure people

1 can actually do that, then the warrant is misleading.

2 DR. KONSTAM: Cindy?

3 DR. GRINES: Yes, I'm all for having  
4 creatinine clearance mandatory, but also the follow-up  
5 ECG, I think, will have to be considered, and this  
6 three day hospitalization. 75 percent of the Torsade  
7 apparently occurred in-hospital, and somebody said,  
8 you know, maybe you can discharge them earlier than  
9 three days, but we don't know that, we haven't seen  
10 actually when the Torsade is occurring in hospitals.

11 So -- I mean, those are the three big  
12 things that I think will be important.

13 DR. KONSTAM: Tom?

14 DR. GRABOYS: Nothing to add.

15 DR. KONSTAM: Tom Bigger?

16 (No response.)

17 DR. KONSTAM: Ileana?

18 DR. PIÑA: I am as concerned about  
19 physicians not doing creatinine clearance calculations  
20 as I am about improper measurement of QTs, specially  
21 when you have a patient with afib where the R/R  
22 interval is varying all over the place, and they may

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1 not know which R/R interval to pick, to measure the  
2 QT, and I heard the sponsor, who had given the, I  
3 think, mandate or suggestion in the protocol that  
4 there be, you know, X number of R intervals measured,  
5 and then an average taken.

6 So I don't know how tight you can get in  
7 the recommendations to put something about the QT.  
8 But I think it can't be ignored.

9 And I think it may at least remind  
10 physicians that they need to do it, and if they don't  
11 know how to do it, maybe they will go find out how to  
12 do it, and do it right.

13 DR. KONSTAM: Joan?

14 DR. LINDENFELD: I think there needs to be  
15 some reminder, some stimulus, I'm just not sure what  
16 it is. It will be easy in the hospital, you can just  
17 put in a policy that you have to order Dofetilide with  
18 a creatinine clearance, and check the QT three hours  
19 later, in-hospital will be easy.

20 I think the harder thing will be out-  
21 patient, I don't know what it is.

22 DR. KONSTAM: I guess I just want to add,

1 to say that every -- to the degree with which we've  
2 developed a comfort level around the safety issues  
3 here, we've done so in the context of dosing and  
4 monitoring, as has been done in the clinical trials,  
5 and therefore I think it is forging new ground.

6 But I think we have to forge that ground,  
7 and I think we have to say that if we don't do it that  
8 way, we have no idea what the risk is going to be, and  
9 we should make every effort to do that, and I'm not  
10 sure that we have really answered exactly how we are  
11 recommending to do it.

12 I think there were a couple of different,  
13 the point about -- and I would add to what has been  
14 said, maybe somebody did say, that we should do  
15 something specifically to assist in the calculation of  
16 the creatinine clearance. And I don't know exactly  
17 what that is going to be.

18 We heard about nomagrams, but something  
19 other than just an educational program. And I would  
20 like to see some kind of a surveillance of how  
21 effective whatever program that has come up with is.

22 I guess I would add, in spirit, that I

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1 would like to try to do that without persuading people  
2 that Quinidine is more safe than Dofetilide. So I'm  
3 not sure exactly how to do that, too.

4 DR. LIPICKY: I guess I would just like to  
5 get a feeling for whose responsibility you think that  
6 is. That is, is it FDA's responsibility to be sure  
7 that doctors use every drug that is approved,  
8 correctly; and should they have some kind of an  
9 inspection system that goes through the hospitals and  
10 looks at prescriptions, and stuff like that; and then  
11 sues them or something, if they are not doing it  
12 right?

13 Whose responsibility is this, where does  
14 the state society fall into this, where do medical  
15 schools fall into this, where do the attending  
16 physicians fall into this?

17 It is not clear to me that you have made  
18 a -- although I don't disagree with anything that has  
19 been said, it is not clear to me why it suddenly is  
20 FDA's responsibility to ensure that doctors use the  
21 drugs properly.

22 And I know one shouldn't sort of say here

1 is a car, drive carefully, you know? That is not  
2 being responsible.

3 On the other hand it isn't clear to me  
4 that outside of some really -- whose responsibility  
5 this is. And you have just laid it at FDA's feet. I  
6 don't know if you did that inadvertently, or  
7 purposely.

8 DR. LINDENFELD: Ray, I personally feel  
9 that it is a physician responsibility to make choices,  
10 and to take the responsibility of the consequences of  
11 those choices. However, in hospitals, and in medical  
12 schools, there are overseeing committees of the proper  
13 use of drugs.

14 JCAH, Joint Commission, comes down very  
15 hard on pharmacy and therapeutics committees that  
16 don't have drug usage and evaluation committees, so  
17 this is --

18 DR. LIPICKY: I understand, but in your  
19 response to this question you just laid it at FDA's  
20 feet, and we are going to try to do something. Bob?

21 DR. TEMPLE: Not entirely FDA's. I think  
22 they've asked us to make sure the company puts in

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1 place labeling and facilitating efforts that might  
2 make it happen, whether we should be sending letters  
3 to people is another question.

4 For what it is worth, a lot of people are  
5 raising questions just like this. You know, there  
6 have been publications citing 100,000 adverse drug  
7 reaction deaths per year, and there is at least some  
8 implication that this is our fault.

9 We don't entirely believe that, we think  
10 it is, you know, everybody else's fault. But the  
11 question could arise, can labeling maneuvers, patient  
12 labeling, and other things, make that better?

13 And we are actively thinking about this.  
14 For what it is worth, when we hear about a mixup,  
15 because people don't realize how many milligrams there  
16 are in a vial, and they inject the whole vial instead  
17 of some smaller amount, we feel obliged to make sure  
18 the labeling is changed right away. The company does  
19 it, of course.

20 So that those mixups won't happen, even  
21 though you could say if people were paying reasonably  
22 adequate attention, those mixups wouldn't have

1 occurred.

2 So we and the people we regulate have at  
3 least some role in that, I would say, and there is a  
4 lot of public discussion about how much of that role  
5 everybody has, and how much we should be doing.

6 DR. KONSTAM: Tom?

7 DR. GRABOYS: We come as a body to advise,  
8 and there is a whole host of kind of sociologic, and  
9 ethical, and moral issues here that obviously come  
10 out.

11 The fact is that I think the sponsor has  
12 to put the fear of God into the user of the drugs, the  
13 physician, that all these terrible things could  
14 happen, and therefore it is the physician's  
15 responsibility, but it is clearly the sponsor's  
16 responsibility, and the FDA's responsibility to enact  
17 this.

18 DR. KONSTAM: You know, I would like to  
19 answer it a different way. I think if you are really  
20 serious about influencing serious about influencing  
21 physician behavior, and if you feel like it is the  
22 FDA's role to influence physician behavior then,



1 really, I don't know how you would do it without  
2 having some way of judging the effectiveness of what  
3 you've done to influence that behavior, otherwise you  
4 have no idea what the impact is.

5 DR. LIPICKY: But if I said I don't think  
6 that is FDA's role, then what?

7 DR. KONSTAM: Should we ask that as a  
8 formal question of the panel?

9 DR. LIPICKY: You might. You really want  
10 me to influence what you do in your practice of  
11 medicine, is that what you are saying?

12 DR. TEMPLE: Ray, the trouble is we do it  
13 all the time.

14 DR. LIPICKY: I understand that. But this  
15 is -- we do it by making things available. They are  
16 asking, at the moment, for us to do things that are  
17 directive, thou must not, or thou shalt --

18 DR. TEMPLE: In the form of labeling that  
19 says that, and in the form of urging the sponsor to  
20 provide some way of calculating creatinine clearance,  
21 fairly conventional methods, if a little more  
22 aggressively --

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1 DR. LIPICKY: Well, if it is limited to  
2 that, that is okay. But that, you know, how do we  
3 know that that influences anything?

4 DR. TEMPLE: Perhaps asking the sponsor to  
5 visit some hospitals and see how it is going. Those  
6 are all within the range of things that have been  
7 done.

8 DR. LIPICKY: Where do medical schools  
9 fit into this whole business of sort of making sure  
10 that physicians know what they are doing. Why does it  
11 all fall on drug companies?

12 DR. KONSTAM: I just want to say that I'm  
13 beginning to sense a certain degree of lethargy by the  
14 panel, so -- you guys are -- so the question -- I  
15 mean, we will take it as far as -- have we helped you  
16 enough on this, or not?

17 DR. LIPICKY: Yes, you have, indeed.

18 DR. KONSTAM: 8C, what recommendation if  
19 any should be made in labeling as to anticoagulation  
20 during sinus rhythm in patients who have been  
21 converted from chronic atrial fibrillation and are  
22 being maintained on Dofetilide?

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1 Peter?

2 DR. KOWEY: None.

3 DR. KONSTAM: Cindy?

4 DR. GRINES: I believe that they maintain  
5 anticoagulants in the atrial fibrillation trials. Is  
6 that correct? And so I --

7 DR. KOWEY: In the firm the design is that  
8 the investigators are not really told to discontinue  
9 anticoagulants. So it is not mandated, necessarily,  
10 but they are not told to stop.

11 Let me just amplify it. I was probably  
12 being a little flip in just saying none. But this is  
13 another area where we don't have enough signs to  
14 answer this -- there is no signs to answer this  
15 question, there has never been a study to answer this  
16 question.

17 And so it really isn't fair to answer this  
18 question for Dofetilide when we don't know about any  
19 other antiarrhythmic drug. So it is just -- it really  
20 would be a quagmire to get into this. I think it is  
21 just leave it alone.

22 DR. GRINES: Yes, bargaining unit don't we

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1 have guidelines on conversion of atrial fibrillation  
2 and anticoagulation? I mean, we could merely quote  
3 the guidelines, or quote the fact that in these trials  
4 we --

5 DR. LIPICKY: We don't write textbooks  
6 that have clinical gospel in them.

7 DR. GRINES: Well, we have a lot of  
8 doctors who don't know these things.

9 DR. LIPICKY: I understand. That is your  
10 problem, not ours.

11 DR. TEMPLE: Well, Ray, we could certainly  
12 be describing what was done in this population, and if  
13 it is of concern say that it is not known that it is  
14 safe to stop anticoagulants. I mean, there are some  
15 things one could do to describe your lack of  
16 knowledge.

17 DR. LIPICKY: It is also not known that it  
18 is safe to continue them. So we should say it is just  
19 unknown, not that some one part is unknown.

20 DR. TEMPLE: Well, anticoagulants are  
21 known to prevent serious consequences in atrial  
22 fibrillation.

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1 DR. LIPICKY: Only if you get your I&R  
2 measured at weekly intervals in your local I&R shop.  
3 And if you don't do that, you are in real trouble.

4 DR. KONSTAM: Can I just -- I mean, this  
5 strikes me, the question seems not quite in place. I  
6 mean, you know, if the question is should the FDA --  
7 should the panel recommend a set of guidelines on  
8 anticoagulation in atrial fibrillation, wouldn't we  
9 want to spend a day discussing that, and put some data  
10 into it?

11 DR. LIPICKY: Or longer. The full  
12 expectation was, Peter's answer is none.

13 DR. GRINES: Well, I don't know, I think  
14 if we are going to make a recommendation about --

15 DR. LIPICKY: Okay, but we thought we  
16 would give you some --

17 DR. GRINES: -- QT intervals, why not make  
18 one about anticoagulation? That is the standard, to  
19 anticoagulate when you are cardioverting somebody, and  
20 continue that anticoagulation after --

21 DR. LIPICKY: But you have no information  
22 to give any recommendation on the basis of. There is

1 nothing in these trials.

2 DR. GRINES: Not in these trials, but in  
3 atrial fibrillation trials.

4 DR. LIPICKY: That is the only trials we  
5 have to write Dofetilide's label with. We are not  
6 going to, I don't think, or maybe we will, I should  
7 ask Bob, we are not going to talk about how you can  
8 avert stroke with anticoagulants in Dofetilide's  
9 label.

10 DR. TEMPLE: No, you don't have to do  
11 that. The only point that seems pertinent here is  
12 that it might be worth telling people we don't know.  
13 If your patients were already on anticoagulants, we  
14 have no information about whether --

15 DR. LIPICKY: As to whether to continue  
16 them or not.

17 DR. TEMPLE: -- while you are using this  
18 stuff it is okay to stop them, we just don't know.

19 DR. LIPICKY: Or whether you should  
20 continue them or not.

21 DR. TEMPLE: We don't know --

22 DR. LIPICKY: We don't know either one of

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1 those.

2 DR. TEMPLE: Right, right. But it would  
3 be worth telling people that, I think.

4 DR. KONSTAM: Can I ask the panel? Peter  
5 said no, I think Cindy said no.

6 DR. GRINES: Wait, I didn't say no.

7 DR. KONSTAM: You didn't say no?

8 DR. GRINES: No, I think you need to --

9 DR. KONSTAM: You didn't say no?

10 DR. GRINES: No, I think you need to --

11 DR. KONSTAM: You said yes?

12 DR. GRINES: I think that if everyone of  
13 these trials they anticoagulated them before -- for 14  
14 days beforehand, plus they continued anticoagulants.  
15 For us not to even mention that, I don't think is  
16 right.

17 DR. KONSTAM: Okay. Tom?

18 DR. GRABOYS: No. I don't think we have  
19 to deal with it.

20 DR. KONSTAM: Tom?

21 DR. BIGGER: None, but it is a conundrum,  
22 really, but I would trust Bob and Ray to come up with

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1 the right words for it.

2 DR. KONSTAM: Ileana?

3 DR. PIÑA: I wouldn't make any specific  
4 recommendations, but I do think, as Bob said, you can  
5 say in the study anticoagulation was continued,  
6 period. In other words, exactly describe what was  
7 done here, and that is it, and leave it at that.

8 DR. LINDENFELD: I agree with what Ileana  
9 just said.

10 DR. KOWEY: Is it in anybody else's  
11 labeling, Ray? No.

12 DR. LIPICKY: Well, I don't know that any  
13 of the trials -- you know, there is only one other  
14 drug, and I don't know that the Quinidine --

15 DR. KOWEY: -- and Flecainide?

16 DR. LIPICKY: No, it --

17 DR. KOWEY: It is for PAF. But I'm  
18 saying, is there any data about anticoagulation in any  
19 drug like that?

20 DR. LIPICKY: No. Well, it wouldn't be in  
21 the PAF stuff, and Quinidine is the only --

22 DR. PIÑA: I don't think the first PAF

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1 trial was out when Flecainide was approved.  
2 Flecainide was approved before the first PAF trial  
3 data would have come out.

4 DR. KONSTAM: I am going to answer no, but  
5 I'm going to do it with discomfort, because I think  
6 that there might well be something to say about this,  
7 and I'm not prepared to say it.

8 And I think that if you like -- if we want  
9 to address this seriously, I mean, I would propose  
10 that we do it with some data in front of us, and have  
11 some discussion about it.

12 9, if Dofetilide is approved, what if any  
13 post-marketing commitments, interaction studies,  
14 studies in special populations, head to head  
15 comparison trials should be sought from the sponsor.

16 Peter?

17 DR. KOWEY: The FDA, by the way, did a  
18 very nice job of summarizing things in the background  
19 package that we received. And one of the things that  
20 Shaw Chen said in his review was that it would be nice  
21 to have, it would be nice to tell the sponsor to go  
22 out and do a head to head comparison with Quinidine.

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1           Somebody has to do that, but it is a  
2           daunting task, and I don't think that we should make  
3           that a condition for approval, and I don't think we  
4           should necessarily mandate a post-market. I think  
5           somebody should do that study someday.

6           But the studies t I think are more  
7           important, and can be done, and should be done post-  
8           marketing are interaction studies. I'm still very  
9           uncomfortable with what we know and what we don't know  
10          about patients who -- specially patients with renal  
11          impairment who receive poly-pharmacy.

12          And I think there is a whole -- I don't  
13          think we have time to really get into all the  
14          individual trials they could carry out, but I think  
15          that there are clearly some that probably need to be  
16          done.

17          DR. LIPICKY: By drug interaction do you  
18          mean pharmacokinetics?

19          DR. KOWEY: Pharmacokinetics.

20          DR. LIPICKY: Not pharmacodynamics?

21          DR. KOWEY: Not pharmacodynamics,  
22          pharmacokinetics interaction studies.

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1 DR. KONSTAM: Cindy?

2 DR. GRINES: I agree.

3 DR. KONSTAM: Tom?

4 DR. KONSTAM: Yes, I agree. And until  
5 they are done, I think this part of the label should  
6 be pretty conservative. And that would, you know,  
7 motivate the studies that probably will make things  
8 more encouraging when you see some results.

9 But I think that is an area where there  
10 were concerns all day, and I think the kind of things  
11 that they agreed they ought to do, and we talked  
12 about, are in the minutes already.

13 DR. KONSTAM: Ileana?

14 DR. PIÑA: Yes, I think the drug/drug  
15 interactions and pharmacokinetics are very, very  
16 critical, because in the real world, particularly the  
17 patients with impaired renal function are going to be  
18 on a lot of other drugs.

19 I would personally love to see a head to  
20 head comparison with Amiodarone and heart failure  
21 patients, because that is a very commonly used drug  
22 today in heart failure for afib, and for other

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1 reasons.

2 And you have this nice Diamond data, and  
3 I think that would be a great study.

4 DR. BIGGER: It would be nice to have in  
5 your label, someday, that we are better than  
6 Amiodarone, that would be a nice thing to have in  
7 there.

8 DR. KONSTAM: Joan?

9 DR. LINDENFELD: I agree we need to know  
10 some more drug data, specifically we've discussed  
11 Toltizim, I think that we have to know, and we may  
12 need to know that even before the drug is out, that is  
13 such a common drug.

14 But you can decide that. But I think the  
15 one that hasn't been mentioned, fluoxetine and  
16 paroxetine, they are commonly used anti-depressants  
17 that do have some 3A4 interaction. Since they are so  
18 commonly used I think we should know that.

19 DR. KONSTAM: Yes, I want to agree. I  
20 think the additional information about drug/drug  
21 interactions I think is mandatory in all of the ways  
22 in which potential drug interactions have been

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1 identified, decytochrome 3A4 and issues of renal  
2 effects, and absorption.

3 And I think I would like to see more data  
4 with regard to all of those possibilities. And I also  
5 want to agree with Ileana's point about heart failure.

6 You know, I was just thinking that  
7 actually the medical reviewer suggested that we  
8 consider approving the drug in heart failure, as the  
9 population to approve it in. And at first that was a  
10 little tempting to me, but then I was thinking we  
11 actually don't know the efficacy of this drug in heart  
12 failure, and particularly since, again, the dosing  
13 regimen that was used in the Diamond heart failure  
14 study was different from in the populations where  
15 efficacy was documented.

16 So I think -- and that is a population in  
17 which we have the most to gain in terms of clinical  
18 effects, perhaps.

19 So I would like to see that. Bob?

20 DR. TEMPLE: You actually do have a little  
21 data from the Diamond component. Those people with AF  
22 were in heart failure. And they responded to a lower

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1 dose. The other thing I will say is that we will  
2 certainly urge further examination of the population  
3 kinetic data base, especially to look for two factors  
4 at once, and they are plainly capable of doing that.

5 That will, I'm sure, give us some of the  
6 answers we are looking for.

7 DR. KONSTAM: Bob, correct me if I'm  
8 wrong. I don't think we know, somebody I'm sure will  
9 correct me, I don't think we know the efficacy with  
10 regard to effect on atrial fibrillation in the Diamond  
11 heart failure trial.

12 What we know is that there was a reduction  
13 in hospitalizations?

14 DR. TEMPLE: They do have data, it is like  
15 47 percent at six months.

16 DR. RYDER: Dr. Konstam, we have data on  
17 two populations, one is the population who had atrial  
18 fib, the 50 patients, and then a certain proportion of  
19 them who are receiving Dofetilide or placebo went into  
20 normal sinus rhythm, and then we have the maintenance  
21 data in that population.

22 Shaw Chen refers to that, and the other

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1 component is, there are a few patients, but still it  
2 is different between Dofetilide and placebo of the  
3 other part of the Diamond studies who did not have  
4 atrial fib but developed atrial fib during Diamond,  
5 and there are fewer in the Dofetilide group than in  
6 placebo, but Shaw Chen refers to this, and FDA, as you  
7 said, does examine this data.

8 DR. KONSTAM: Okay, I think we did it.  
9 Thank you.

10 (Whereupon, at 5:23 p.m. the above-  
11 entitled matter was concluded.)  
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**CERTIFICATE**

This is to certify that the foregoing transcript in the  
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Before:                       CARDIOVASCULAR AND RENAL DRUGS  
                                  ADVISORY COMMITTEE

Date:                         JANUARY 28, 1999

Place:                        BETHESDA, MARYLAND

represents the full and complete proceedings of the  
aforementioned matter, as reported and reduced to  
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*Donna Willis*

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---

- 1 -

---

11:08 [1] 130:2  
 11:30 [1] 130:3  
 12-A30 [1] 8:18  
 12:53 [1] 197:11  
 18USC208 [1] 8:14  
 1990s [1] 5:10  
 1:15 [1] 197:10  
 1:30 [1] 198:2  
 1A [7] 18:18; 97:6; 195:4; 314:19; 319:13;  
 322:9; 376:4  
 1B [1] 322:10  
 1C [6] 5:9; 7:12; 18:18, 19; 195:5; 326:8  
 1D [1] 319:5

---

- 2 -

---

2/3 [1] 384:20  
 28th [1] 8:1  
 2A [2] 333:13; 341:18  
 2B [1] 333:17  
 2C [2] 333:21; 342:6

---

- 3 -

---

3A [2] 104:22; 105:1  
 3A4 [8] 80:12; 88:17; 103:5, 16; 104:6;  
 114:15; 420:17; 421:1

---

- 5 -

---

5:23 [1] 423:10  
 5B [3] 369:7; 372:18; 373:3  
 5C [4] 368:10; 369:6; 372:18; 373:3

---

- 6 -

---

6A [2] 378:5, 17

---

- 7 -

---

70s [1] 212:3  
 7th [1] 4:13

---

- 8 -

---

8A [1] 382:16  
 8B [1] 396:10  
 8C [1] 410:18

---

- 9 -

---

9:00 [1] 4:2

- A -

a.m. [4] 4:2; 115:14; 130:2, 3  
 abe [1] 381:15  
 ability [8] 28:4; 94:13; 127:3; 201:7;  
 247:15, 16, 18; 339:1  
 ablation [2] 19:15; 22:5  
 ablative [1] 23:6  
 able [13] 61:4, 5; 62:13; 89:7; 104:16;  
 119:1; 200:12; 264:7; 291:2; 297:6; 313:8;  
 375:17; 387:3  
 abnormal [3] 77:16; 82:19; 346:3  
 abnormalities [1] 4:20  
 abnormality [4] 6:3; 275:8; 312:4; 345:19  
 abnormally [1] 93:9  
 above-entitled [3] 130:1; 197:11; 423:10  
 absence [9] 122:1, 3; 158:1; 171:17;  
 194:9; 287:17; 361:9; 380:18, 21  
 absolute [9] 15:11; 34:4; 55:18, 20; 81:11,  
 12; 219:2; 224:13; 280:15  
 Absolutely [3] 26:15; 215:1; 379:20  
 absolutely [11] 28:2, 22; 54:5; 56:12;  
 121:2, 18; 229:22; 280:12; 306:22; 307:6;  
 368:15  
 absorption [8] 34:15, 17, 19, 22; 43:14;  
 89:2, 13; 421:2  
 abutting [1] 128:8  
 AC50 [1] 71:7  
 academic [2] 9:14; 127:17  
 academics [1] 106:20  
 accelerated [1] 300:14  
 accept [3] 28:13; 41:8; 274:4  
 acceptable [5] 130:10; 300:1; 338:2;  
 378:20; 388:18  
 access [3] 4:13, 21; 353:16  
 accompanying [1] 17:19  
 accordance [2] 8:14; 396:12  
 according [20] 46:15; 66:5; 79:4; 108:8;  
 134:5; 144:8; 152:11; 211:3, 15; 216:10;  
 220:4; 262:5, 17; 263:8; 265:20; 307:4;  
 365:4, 5, 6; 367:14  
 account [6] 46:6; 50:3; 57:20; 241:10;  
 356:19; 358:17  
 accounted [1] 36:20  
 accounting [7] 35:20; 40:14; 44:7; 45:5, 6,  
 8; 192:11  
 accounts [3] 33:18; 73:10; 75:9  
 accumulation [1] 256:12  
 accurate [1] 30:9  
 accurately [1] 345:3  
 ace [2] 137:14; 140:2  
 achieve [4] 70:3; 137:1; 274:8; 297:6  
 achieved [2] 45:14; 49:20  
 achieving [1] 140:11  
 acknowledge [3] 9:6; 156:15; 299:16  
 Act [2] 4:13; 339:3  
 Acting [1] 4:4  
 acting [2] 100:6; 230:10  
 action [4] 22:19; 72:5; 281:21, 22  
 active [8] 135:15, 16; 348:8; 349:7, 11, 16;  
 350:7, 18  
 actively [4] 38:6; 90:17; 391:15; 407:13  
 activity [5] 27:20; 40:18, 19; 118:17; 310:9  
 actor [2] 106:13; 301:18  
 actual [5] 136:19; 139:15; 204:9; 216:8;  
 277:4  
 acute [10] 132:6; 326:9, 12, 16, 20; 333:8,  
 15; 360:18; 361:4; 366:3  
 acutely [3] 28:1; 200:2; 327:6  
 ad [1] 127:17  
 add [19] 6:7; 88:3; 117:10; 123:18;

178:13; 201:11; 202:13; 249:15; 277:10;  
 310:12, 13; 354:5; 357:11, 16; 375:6;  
 402:14; 403:22; 404:13, 22  
 added [3] 118:10; 154:17; 177:20  
 addendum [4] 107:21; 108:11, 13; 111:2  
 adding [1] 166:4  
 addition [12] 8:20; 10:2; 13:5; 14:17; 39:9,  
 17; 43:6; 168:6; 193:19; 197:1; 222:15;  
 348:13  
 Additional [1] 199:20  
 additional [10] 104:1; 110:7; 155:12;  
 172:9; 179:1; 195:8, 10; 212:12; 288:14;  
 420:20  
 additive [4] 117:9; 118:3, 6, 12  
 address [18] 10:12; 24:18; 37:6; 39:5;  
 81:19; 91:18; 92:6; 93:13; 94:21; 170:22;  
 177:3; 186:3; 239:3; 279:8; 311:3; 337:7,  
 14; 417:9  
 addressed [6] 64:4; 102:9; 255:17;  
 296:18; 316:12; 358:13  
 addresses [1] 8:3  
 addressing [4] 26:14; 86:16; 188:16;  
 340:10  
 adds [1] 200:8  
 adequate [6] 5:1; 220:14; 225:7; 349:9;  
 397:10; 407:22  
 adequately [1] 376:11  
 adhere [1] 377:17  
 adherence [1] 174:9  
 adjust [5] 77:4; 136:17; 316:2; 358:8, 20  
 adjusted [21] 45:18; 46:4; 100:3; 132:15;  
 137:1; 139:12; 143:10, 12; 152:13; 157:4,  
 5, 14; 161:13; 169:15; 260:5; 263:8;  
 266:6; 284:10, 16; 294:15; 336:3  
 adjusting [2] 219:6; 316:9  
 adjustment [34] 35:11; 36:22; 37:5; 45:16;  
 46:10; 47:3, 9; 50:6, 8; 62:1; 70:10;  
 143:17, 20; 154:20; 155:7, 14; 160:21;  
 161:5; 165:1; 166:5; 184:12; 218:13;  
 219:4, 9, 10; 255:14; 263:16; 266:5;  
 278:12; 284:17; 294:12; 323:3; 356:19  
 adjustments [7] 157:15; 161:2, 8; 218:21;  
 307:3; 359:7, 21  
 adjusts [1] 46:5  
 administer [3] 211:9, 10; 212:5  
 administered [3] 210:21; 228:9; 365:16  
 administering [1] 202:12  
 admission [1] 251:12  
 admit [1] 236:4  
 admitted [2] 23:14; 376:7  
 admittedly [1] 317:18  
 admonitions [1] 264:9  
 advance [1] 195:11  
 advanced [5] 20:20; 25:1; 140:4; 195:19;  
 196:17  
 advantage [1] 329:22  
 adverse [19] 65:11; 86:3; 153:17; 169:8,  
 14, 19; 174:2, 12; 190:6; 191:17; 192:7,  
 12, 18; 301:20; 334:19; 340:8, 15; 369:21;  
 407:6  
 adversely [1] 353:10  
 adversity [1] 353:5  
 advice [2] 239:7; 358:12  
 advise [3] 164:15; 231:18; 408:7  
 advised [1] 220:21  
 advising [1] 302:4  
 Advisory [5] 4:14; 6:21; 11:15; 32:18;  
 130:16  
 advocate [1] 245:9  
 advocated [2] 240:2; 276:16  
 affect [11] 38:7; 49:4; 66:20; 90:2; 92:8;

94:13; 109:21; 184:10; 357:3; 359:10; 373:18  
 affected [4] 35:10; 118:10; 348:6; 353:10  
 affecting [4] 14:21; 43:14; 118:7, 18  
 affects [3] 17:22; 21:10; 393:13  
 affinity [2] 40:20; 41:2  
 Afib [6] 24:18; 30:20, 22; 31:2, 7; 98:18  
 afib [6] 31:11; 315:11; 329:2; 395:21; 402:21; 419:22  
 afternoon [2] 153:5; 245:10  
 afterwards [1] 333:2  
 age [25] 15:3, 5, 6, 7; 32:1, 9; 44:5; 77:10, 19; 78:18, 20; 79:16, 17; 80:1; 133:6; 137:4; 143:5; 145:5; 156:11; 157:14; 175:21; 185:19; 275:2, 15, 21  
 Agency [5] 8:18; 91:17; 186:20; 188:4; 283:8  
 agenda [4] 7:20; 8:7; 10:6; 13:8  
 agent [13] 20:8, 19; 25:7; 178:19; 184:14; 188:9; 191:5; 193:11; 195:10; 224:11; 303:1; 308:19; 401:15  
 agents [22] 13:2; 19:20; 20:5, 12, 17; 21:5; 126:16; 179:7, 18; 180:8; 184:6, 10, 16; 185:5; 186:6; 194:4; 195:4; 196:3, 7; 289:13; 314:19; 374:14  
 aggressive [3] 28:13; 29:2; 310:18  
 aggressively [1] 409:22  
 agonizing [1] 84:20  
 agree [47] 22:4; 26:12; 29:22; 31:16; 108:14; 113:2, 7; 123:17; 180:4; 195:5; 209:16; 273:21; 275:9; 282:22; 283:18; 290:19; 306:19; 312:17; 321:12; 335:18; 338:5; 344:6; 347:21; 350:3, 6, 16, 22; 351:6, 7; 357:5; 372:12; 373:8; 374:2; 376:9, 13; 377:13; 378:18; 382:14; 384:21; 386:19; 389:18; 416:8; 419:2, 4; 420:9, 19; 421:5  
 agreed [5] 354:7; 381:11; 391:4, 5; 419:11  
 agreement [3] 344:7; 354:12; 356:8  
 agrees [2] 333:14; 337:17  
 ain't [1] 237:3  
 albeit [1] 177:8  
 algorithm [48] 46:16; 76:14; 132:21; 134:6; 143:7; 144:9; 152:11, 14; 154:15, 17; 155:4; 160:21; 163:12; 165:2; 166:2, 4, 8; 169:1, 6; 172:5, 11, 17; 174:10; 184:12; 196:11; 213:3, 21; 214:3; 215:4, 9; 216:10; 218:1, 5, 6; 220:5; 244:3; 262:6, 12, 13, 18; 263:8; 265:19; 278:11; 292:15, 16; 294:8, 11; 316:8  
 algorithms [1] 158:19  
 alive [2] 32:6, 8  
 All-cause [2] 159:16; 163:17  
 all-cause [8] 158:20; 170:11; 180:16; 183:11, 13; 188:20; 189:20; 193:2  
 allow [7] 9:20; 117:17; 170:22; 263:14; 303:13; 319:6; 387:13  
 allowed [7] 4:21; 11:21; 12:4; 218:14, 21; 263:21; 374:9  
 allowing [3] 36:21; 233:15; 300:15  
 allows [1] 35:15  
 alone [4] 14:22; 173:15; 240:17; 411:21  
 alongside [1] 119:11  
 alter [3] 22:19; 65:16; 302:12  
 alteration [1] 103:15  
 Alternatively [1] 53:8  
 alternatively [1] 90:1  
 alternatives [1] 125:12  
 alters [1] 326:12

Amantadine [1] 90:20  
 amazing [1] 129:16  
 Amelorida [1] 90:18  
 amelorida [2] 67:1, 2  
 amendment [9] 172:21; 173:2; 213:13; 246:21; 247:2, 4, 6, 9; 253:7  
 Amiodarone [28] 19:2; 20:17, 19; 23:22; 24:21; 60:13; 97:9; 120:20; 125:16; 126:13; 127:10; 180:6; 185:6, 12; 189:17; 190:18; 193:4, 10; 194:12; 196:19; 280:16; 305:16; 306:12; 311:16; 315:18; 376:5; 419:20; 420:6  
 amount [4] 10:17; 13:1; 198:5; 407:17  
 amounts [1] 42:7  
 amplify [1] 411:11  
 Amuterine [1] 349:14  
 Anafrodit [2] 301:11, 14  
 analogy [3] 306:19; 307:6; 317:20  
 analyses [3] 161:19; 348:11; 351:11  
 Analysis [3] 44:4; 148:22; 156:4  
 analytical [1] 117:14  
 analyzed [6] 43:18; 93:19; 149:17; 161:11; 342:3; 348:12  
 analyzing [2] 192:14; 348:15  
 anatomic [1] 47:18  
 ANDREWS [5] 207:14; 249:14, 20; 250:2, 7  
 Andrews [3] 207:12; 239:2; 249:13  
 anecdote [2] 301:9; 302:7  
 angina [4] 132:7; 162:13, 14; 226:19  
 announcement [1] 8:3  
 announcements [1] 7:21  
 annual [1] 23:11  
 answered [5] 243:13; 334:10; 339:15; 381:4; 404:10  
 answering [2] 345:5; 369:11  
 answers [5] 238:17; 243:19; 372:3; 391:1; 422:6  
 anti-depressants [1] 420:16  
 anti-hypertensive [1] 363:11  
 antiarrhythmic [30] 5:7, 9; 7:12; 12:9; 16:16; 18:16; 20:11; 21:5; 26:2; 60:12; 123:20; 158:8; 170:18; 184:10; 186:6, 19; 188:5; 189:21; 190:2; 191:11; 194:20; 196:7, 20; 229:15; 289:13; 310:20; 345:22; 349:12; 411:19  
 antiarrhythmics [4] 313:19; 314:17; 352:19; 372:2  
 antibiotics [1] 52:17  
 anticipate [1] 89:4  
 anticoagulant [1] 28:15  
 anticoagulants [9] 28:8; 387:19; 411:5, 9; 412:14, 20; 414:8, 13; 415:14  
 anticoagulate [2] 31:8; 413:19  
 anticoagulated [5] 136:2; 199:11, 12, 17; 415:13  
 anticoagulation [13] 26:9; 28:14; 29:2, 12; 199:19; 310:13; 410:19; 412:2; 413:8, 18, 20; 416:5, 18  
 antihistamines [1] 99:16  
 anxiety [1] 111:20  
 anybody [14] 61:4, 6; 124:9; 277:7; 288:8; 352:20; 360:8; 363:15; 364:17; 368:18; 379:22; 391:11; 399:6; 416:10  
 anyway [7] 60:14; 61:20; 71:20; 222:22; 285:14; 370:15; 372:10  
 anywhere [3] 209:14; 255:18; 325:8  
 apart [1] 113:14  
 apologize [4] 174:20; 192:21; 227:13; 266:17  
 apparent [4] 6:10; 47:7; 149:6, 11

Apparently [1] 241:13  
 apparently [1] 402:7  
 appear [7] 73:6; 95:5; 97:22; 264:18; 336:12; 357:7; 380:13  
 appearance [2] 8:6, 12  
 appeared [2] 192:9, 17  
 appears [5] 41:20; 47:13; 95:21; 189:1; 366:22  
 appendix [2] 146:5; 164:10  
 applicable [3] 19:9; 366:1, 3  
 application [2] 30:16; 325:3  
 applications [1] 188:5  
 applied [1] 47:9  
 applies [1] 29:13  
 apply [3] 185:17; 340:19; 364:22  
 Applying [1] 140:20  
 applying [1] 141:3  
 appreciate [3] 162:19; 267:10; 298:15  
 appreciated [5] 16:6, 10, 14; 18:10; 356:3  
 apprehensive [1] 5:6  
 approach [21] 23:5, 6; 52:22; 69:6, 10; 127:15; 149:20; 154:22; 158:20; 240:2; 281:19; 282:17, 20; 297:6; 357:13, 20; 362:2; 365:11; 372:1; 377:15; 401:9  
 approaches [2] 91:8; 365:9  
 approaching [2] 61:1; 319:5  
 appropriate [8] 70:10; 82:15; 154:15; 170:18; 196:15; 305:18; 359:20; 370:9  
 appropriately [3] 177:4; 216:9; 277:5  
 approvability [3] 297:3; 299:1, 5  
 approvable [4] 313:10; 381:21; 383:13, 22  
 approval [10] 7:2, 6; 17:12; 128:6; 300:14, 15; 338:11; 382:18; 390:6; 418:3  
 approve [20] 91:4; 100:17; 262:11; 263:7; 270:10; 300:20; 314:9; 316:18; 351:15; 381:18; 382:2; 383:8; 385:16; 386:3; 389:14; 390:15; 421:9  
 approved [30] 4:19; 6:15, 22; 7:10, 11; 13:2; 19:3, 20; 20:8; 24:1, 9; 91:5; 127:13; 128:14, 18; 289:12; 301:11; 338:13; 354:16; 355:10; 381:14, 16; 382:5; 384:6; 385:8; 390:4; 405:7; 417:1, 2, 12  
 approving [4] 220:19; 313:16; 315:6; 421:8  
 approximate [1] 42:8  
 approximately [15] 16:2; 35:7, 18; 36:17; 49:11; 51:3; 55:13; 131:17; 137:5; 151:13; 164:8; 179:10; 208:4; 248:14; 320:12  
 approximation [1] 214:11  
 area [12] 39:11, 22; 85:22; 94:7; 95:3; 96:13; 157:19; 283:7; 355:17; 359:20; 411:13; 419:9  
 aren't [5] 60:19; 95:14; 114:6; 318:17; 342:4  
 argue [6] 29:9; 235:20; 240:16; 245:10; 337:20; 388:16  
 argument [5] 59:6; 281:6, 15; 337:22; 384:19  
 arguments [1] 240:20  
 arise [1] 407:11  
 arisen [1] 307:15  
 arises [3] 124:6; 181:20; 265:8  
 arm [5] 227:15; 271:19; 303:7; 375:15; 376:18  
 armamentarium [1] 197:2  
 arms [4] 137:17; 244:7, 17; 364:2  
 arose [1] 255:16  
 arrest [1] 325:18  
 arrhythmias [8] 5:14; 7:11; 12:19; 15:22; 64:10; 338:12; 371:14; 372:14  
 arrhythmic [11] 160:10, 14, 16; 189:3;

286:17; 287:14; 288:3, 5; 290:11, 14, 20  
 arrhythmia [25] 5:8, 10; 6:5; 7:10; 14:13;  
 15:14, 21; 17:1; 18:22; 19:16; 44:5; 132:3,  
 8; 135:5; 145:4; 147:21; 152:15; 190:9;  
 229:20; 287:2; 290:6, 8; 370:18; 371:11;  
 391:21  
 Art [1] 127:21  
 artery [1] 190:12  
 Arthur [1] 9:18  
 article [1] 240:3  
 ascribe [1] 95:8  
 aside [1] 378:11  
 asking [27] 4:5; 63:2; 64:15; 76:13; 83:8;  
 85:1, 2; 101:17; 107:4, 8; 207:1; 230:21;  
 232:3; 234:4; 246:14; 253:2; 258:7; 263:6;  
 276:22; 306:7; 308:8; 327:12; 328:17;  
 331:6; 396:4; 409:16; 410:4  
 aspect [2] 113:5; 342:13  
 aspects [3] 32:22; 47:15; 298:14  
 assay [4] 93:8, 9, 11; 279:6  
 asses [3] 182:14; 188:11; 218:15  
 assess [2] 44:13; 147:21  
 assessed [3] 36:11; 170:9; 266:6  
 assessing [5] 35:13; 39:22; 132:22;  
 279:11, 16  
 assessment [6] 22:12; 30:8; 170:15;  
 187:5; 353:2; 354:4  
 assigned [21] 141:7, 17; 142:20; 156:9;  
 158:16; 159:11; 160:1, 17; 162:4, 7;  
 163:17; 164:5; 166:1, 11; 170:3, 4; 173:9;  
 212:21; 217:5; 229:17  
 assignment [2] 160:13; 164:2  
 assist [1] 404:15  
 associated [23] 13:7; 18:1; 21:10; 25:18;  
 49:1; 84:17; 123:10; 132:9; 159:10; 160:7;  
 166:17; 170:9, 19; 179:16; 183:2, 5;  
 187:22; 189:10; 195:21; 214:5; 290:13;  
 291:5; 301:12  
 associates [1] 157:2  
 association [8] 5:5; 18:7; 137:6; 146:7,  
 19, 22; 167:21; 384:20  
 associations [1] 167:18  
 assume [5] 32:3; 91:11; 117:9; 364:8;  
 386:1  
 assuming [1] 141:2  
 assumption [5] 52:19; 54:10; 117:10;  
 121:5; 395:8  
 assumptions [2] 336:17; 397:15  
 assurance [2] 289:22; 396:5  
 assure [2] 98:12; 273:17  
 assured [1] 287:7  
 asymptomatic [4] 5:21; 26:5; 346:2, 19  
 ATKINSON [26] 22:1; 67:16; 68:1; 69:15;  
 70:1, 9, 17; 72:21; 74:22; 75:21; 77:5;  
 78:9; 95:2, 18; 121:4; 126:14; 261:22;  
 263:5; 264:5; 266:8; 267:4, 16; 304:2, 20;  
 305:3, 8  
 Atkinson [10] 9:18, 22; 51:14; 67:9; 121:3;  
 123:17; 126:8; 261:18; 303:22; 361:5  
 Atrial [3] 14:12, 20; 15:17  
 attach [1] 256:21  
 attaching [1] 256:17  
 attempt [7] 69:1; 156:18; 179:5; 186:4;  
 201:2; 234:14; 310:17  
 attempts [3] 125:3; 156:20; 380:8  
 attending [3] 76:10; 405:15  
 attention [9] 7:15; 34:2; 164:7; 168:9;  
 207:15; 226:16; 367:22; 400:13; 407:22  
 attenuated [1] 183:18  
 Attenuation [1] 49:14  
 attenuation [1] 62:8

attributable [3] 41:11, 12; 286:15  
 attributed [1] 42:9  
 AUC [2] 37:21; 103:3  
 AUCs [2] 93:2; 260:14  
 AUDIENCE [1] 61:21  
 audience [2] 71:6; 398:19  
 augment [1] 234:14  
 authority [1] 300:13  
 authors [2] 6:2, 4  
 automatically [5] 77:22; 217:1, 21;  
 256:22; 331:22  
 AV [2] 132:4; 274:19  
 available [25] 14:10; 16:18; 18:9, 17; 20:2,  
 5; 23:18; 41:9; 179:7; 180:8; 186:6;  
 191:19; 194:19; 279:6; 288:15; 306:11;  
 351:12; 355:14, 17; 378:2, 7, 10, 14;  
 380:8; 409:15  
 average [20] 46:11; 83:9, 17; 86:20;  
 116:19; 122:22; 123:1; 124:5, 12; 127:2;  
 137:4; 175:21; 179:17; 200:21; 201:3;  
 263:4; 270:12, 14; 368:17; 403:5  
 avert [1] 414:8  
 averted [2] 324:13; 334:7  
 avoid [2] 85:3; 261:20  
 aware [5] 10:8; 22:16; 75:6; 284:8; 393:19  
 awareness [1] 76:13  
 awful [2] 67:20; 396:6  
 awfully [1] 75:16  
 Axis [1] 94:18  
 axis [9] 36:8; 49:7, 8; 69:17; 92:10; 93:3;  
 94:14; 150:14, 16

---

- B -

---

B3 [1] 8:14  
 baby [1] 15:11  
 background [4] 33:22; 158:10; 291:14;  
 417:18  
 Backup [5] 79:20; 81:4; 205:7; 261:2;  
 303:14  
 backup [25] 69:16; 74:2; 79:3, 5; 81:10;  
 92:3, 19; 93:19; 94:5, 12; 107:16; 108:20;  
 176:19; 212:19, 20; 213:7; 214:5, 6;  
 216:7; 219:21; 220:1; 272:12; 284:6;  
 288:14, 15  
 backwards [1] 52:11  
 badly [1] 337:16  
 badness [1] 380:17  
 bag [1] 253:15  
 bail [2] 234:1, 2  
 balance [5] 130:11; 318:4; 319:18;  
 354:15; 381:13  
 balanced [1] 32:9  
 ballpark [1] 324:6  
 bands [1] 47:1  
 bank [1] 107:3  
 bar [9] 49:18; 55:5; 62:15; 70:16; 71:16;  
 72:18; 229:6; 299:21  
 bargaining [1] 411:22  
 barring [1] 340:14  
 bars [4] 15:7; 148:10, 12; 364:3  
 base [46] 38:9; 40:6; 42:20; 43:22; 44:4,  
 17; 51:1; 68:21; 80:10; 81:6; 87:6, 15;  
 88:3, 10, 12; 104:14; 106:12; 109:10;  
 126:2; 168:8; 175:15; 185:21; 188:19;  
 189:18; 211:7; 221:2, 6; 278:7; 284:13;  
 285:4; 290:22; 298:5; 314:7; 316:21;  
 317:10;  
 337:10, 11; 342:12; 348:16; 351:21;  
 353:4, 16; 361:9; 389:13; 422:3  
 Based [2] 8:7; 220:16

based [30] 5:3; 35:11; 50:8, 14; 58:5;  
 59:6; 63:19; 67:9; 76:1; 139:4; 158:14;  
 174:1; 187:21; 214:2; 220:14; 229:17;  
 230:13; 266:5; 300:15; 321:5; 330:19;  
 331:12; 332:15; 333:13; 336:14; 342:7;  
 345:21; 352:11; 357:21; 365:10  
 Baseline [3] 163:21; 270:16, 17  
 baseline [23] 49:9; 81:14; 133:1; 137:11;  
 139:13, 17; 143:12; 145:22; 147:3;  
 148:12; 154:9; 156:7; 157:5; 159:8; 163:1;  
 171:20; 176:16; 177:18; 185:19; 218:18;  
 227:1; 271:1, 6  
 bases [2] 88:15; 186:16  
 basic [2] 37:14, 19  
 Basically [1] 62:11  
 basically [20] 52:3; 63:3, 10; 65:1; 91:10;  
 92:20; 94:3, 18; 96:7; 102:5; 109:9; 110:6;  
 202:17; 206:6; 243:8; 250:11; 255:5;  
 318:17; 346:18; 363:15  
 basis [7] 50:6; 51:6; 97:4; 163:13; 320:12;  
 337:18; 413:22  
 bazetts [1] 82:6  
 bear [2] 235:2; 282:8  
 bearing [1] 260:1  
 beat [2] 123:7; 259:11  
 beats [11] 83:5, 9, 12, 17, 20; 97:3; 193:7;  
 261:11; 303:8; 368:16  
 becomes [5] 15:11; 73:11, 12; 74:11;  
 393:4  
 becoming [1] 334:16  
 beds [1] 23:11  
 beforehand [1] 415:14  
 begins [1] 215:14  
 behalf [1] 11:16  
 behavior [3] 408:21, 22; 409:3  
 behold [1] 92:10  
 belabor [1] 186:8  
 Belgium [1] 48:2  
 believable [1] 114:6  
 believe [42] 9:3, 19; 22:7; 53:2; 55:18;  
 71:3, 19; 73:4; 79:22; 122:15; 155:19;  
 164:21; 200:14; 202:5; 219:20; 228:7, 8;  
 245:21; 251:17; 264:12; 279:10; 280:5;  
 281:15; 288:22; 300:6; 302:22; 311:16;  
 313:6; 332:21; 338:18, 21, 22; 371:17, 18;  
 376:22; 377:16; 400:12; 401:2, 6, 11;  
 407:9; 411:4  
 believes [1] 9:5  
 believing [1] 400:19  
 bend [1] 237:10  
 beneficial [2] 84:15; 339:12  
 benefit [48] 12:10; 22:12; 27:2; 123:21;  
 131:3; 149:13; 170:15; 178:19; 179:16;  
 182:7; 188:11; 190:16; 192:6; 223:22;  
 308:13; 309:1; 318:5; 324:11; 325:9;  
 326:17; 329:11; 330:12; 332:18; 333:3,  
 22; 334:2, 5, 20; 336:10; 338:5, 6; 340:4,  
 5;  
 342:19; 345:17, 20; 353:2; 354:4; 365:19;  
 385:4; 386:21; 387:12; 390:12, 19;  
 392:11, 12; 394:19; 395:20  
 benefits [10] 12:5; 29:5; 145:10; 149:11;  
 178:21; 179:5; 319:9; 337:8; 389:16, 19  
 benign [3] 387:18, 20, 21  
 bent [1] 202:12  
 besides [1] 87:3  
 beta [7] 80:6; 140:2; 188:22; 190:14;  
 275:13; 277:10; 318:9  
 bias [2] 58:12; 88:13  
 BIGGER [21] 65:12; 66:14; 277:9; 281:18;  
 292:4; 315:21; 321:9; 331:17; 332:1;

341:2; 350:22; 358:1; 369:17; 372:6;  
378:4; 383:21; 389:12; 395:5, 15; 415:21;  
420:4  
Bigger [4] 65:8; 277:6; 390:14; 402:15  
igger [3] 188:7; 238:18; 368:7  
iggist [6] 53:2; 91:9; 106:1, 7; 116:8;  
363:10  
billion [1] 16:2  
binary [1] 252:7  
bioavailability [4] 34:4, 7, 12, 16  
biology [1] 306:16  
biostatisticians [1] 69:9  
bit [31] 29:18; 58:1; 60:8; 72:22; 88:16;  
93:14; 111:20; 162:21; 179:1; 200:20;  
207:17; 217:9; 227:19; 248:6; 250:6;  
258:5, 12; 260:1; 262:12, 14; 264:9;  
272:20; 291:14; 312:18; 329:15; 335:8, 9,  
12; 375:6; 391:17  
bivariate [1] 364:6  
black [1] 63:7  
bleeding [1] 316:16  
blind [6] 131:19; 135:15; 136:3; 144:13;  
151:19; 158:16  
blinded [3] 160:12; 249:3; 272:1  
block [2] 132:4; 397:9  
blocker [4] 47:17; 275:13; 277:10; 312:15  
blockers [9] 80:7; 140:2; 167:21; 175:12;  
177:15; 190:14, 17; 278:7; 318:9  
blocks [1] 54:8  
blood [25] 35:2; 80:6, 15; 81:15; 87:7;  
89:15; 90:2; 95:9; 115:10; 121:12; 228:1,  
18; 264:20; 265:2, 11; 266:1, 2; 279:6;  
299:20; 305:9, 19; 311:21; 359:15; 361:6;  
396:14  
bloody [1] 123:7  
lue [7] 15:7; 21:5; 39:3; 47:6; 49:11;  
47:6; 149:2  
blush [1] 370:20  
board [3] 201:16; 220:3  
Bob [32] 102:10; 113:11; 115:4; 123:17;  
214:13; 231:20; 254:22; 264:6; 298:22;  
302:10; 308:1; 315:7; 318:14; 323:6;  
326:21; 329:17; 337:4; 345:4; 357:9;  
359:5; 385:14; 387:14; 388:3; 390:21;  
392:3; 396:20; 406:20; 414:7; 415:22;  
416:4; 421:19;  
422:7  
body [9] 44:15; 45:8; 77:20; 130:7, 13;  
132:4; 357:6; 389:22; 408:7  
boil [1] 53:13  
bona [1] 300:1  
book [2] 253:9; 257:17  
booklet [1] 120:8  
books [1] 120:11  
boom [2] 15:11  
Boston [1] 237:8  
bother [1] 255:10  
bottles [2] 176:14; 298:10  
box [5] 46:4; 86:7; 264:10; 364:12, 13  
boxes [1] 86:6  
Brad [2] 82:12; 85:13  
Bradley [1] 304:13  
Brater [7] 13:17; 32:15, 20; 67:11; 127:7;  
178:7; 400:11  
break [6] 125:8; 129:15, 21; 174:17;  
197:6; 235:5  
reakdown [5] 23:12; 272:17; 275:20;  
322:1; 382:19  
breaking [1] 397:1  
breaks [1] 235:17  
breakthrough [2] 234:8; 235:11

breast [2] 232:21; 233:1  
breath [3] 147:22; 148:20; 149:12  
breathe [1] 28:17  
brief [4] 5:3; 14:4, 6; 208:19  
briefing [12] 107:21; 120:8, 11; 134:1;  
141:14; 142:22; 146:4; 207:15, 16; 208:3;  
253:9; 285:16  
briefly [4] 168:5; 169:8; 301:6; 341:18  
bringing [1] 315:22  
brings [4] 74, 2; 198:15; 230:8; 235:20  
broad [2] 16:20; 80:2  
Bromfenex [1] 6:22  
build [1] 373:2  
Building [1] 8:19  
bulk [2] 286:9; 298:3  
BUN [1] 373:17  
bunch [2] 374:21; 395:17  
bunches [2] 235:1; 355:14  
burdensome [1] 301:5  
business [1] 410:9  
busy [2] 77:11; 171:1  
button [2] 331:21; 343:14  
bypass [1] 354:2

---

- C -

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C-max [1] 104:8  
Caco [1] 39:8  
cake [2] 77:1; 81:10  
calcium [5] 167:21; 175:12; 177:14;  
190:17; 275:12  
calculate [4] 77:21; 232:22; 233:1, 5  
Calculated [1] 136:17  
calculated [5] 58:5; 74:4; 133:2; 210:11;  
230:14  
calculating [1] 409:20  
calculation [4] 129:17; 210:3; 358:18;  
404:15  
calculations [5] 70:2; 73:14; 77:12;  
211:16; 402:19  
calculator [3] 233:3, 4, 5  
Califf [19] 4:3; 9:2, 8, 11; 11:14; 14:1;  
32:18; 67:16; 130:15; 153:3; 173:20;  
174:17; 178:15; 219:13; 253:3; 258:8;  
285:15; 323:13; 385:12  
call [13] 31:11; 63:6; 122:4, 12; 164:7;  
168:9; 226:15; 244:13; 258:15; 288:13;  
314:13, 16; 356:9  
CAMIAT [1] 190:19  
Camm [2] 29:22; 30:10  
cancer [2] 232:21; 233:1  
capable [1] 422:4  
captain [2] 197:7; 198:9  
capture [1] 59:3  
captured [1] 135:7  
car [1] 406:1  
cardia [1] 132:4  
Cardiac [1] 48:20  
cardiac [10] 5:9; 18:21; 48:15; 165:4, 5;  
182:1; 190:9; 317:22; 325:18; 386:20  
cardiologist [2] 58:2; 60:6  
cardiologists [1] 176:7  
cardiology [4] 56:11; 64:19; 67:12; 369:21  
cardiomyopathic [1] 370:13  
cardiomyopathy [1] 315:14  
Cardiorenal [1] 11:15  
cardiovascular [4] 33:4; 137:16; 140:4;  
174:3  
cardioversion [15] 28:14; 31:1, 12; 70:19;  
136:9; 200:9; 201:2, 12, 15; 202:13, 20;  
205:19; 320:15; 327:7; 329:5

cardioversional [1] 31:2  
cardiovert [5] 201:11; 328:6, 13; 329:2, 19  
cardioverted [13] 151:6; 200:2, 8, 19;  
201:7, 9, 20; 203:1, 4; 204:16; 209:19;  
248:22; 345:17  
cardioverting [2] 202:12; 413:19  
cardioverts [1] 328:21  
care [3] 21:12; 162:18; 222:3  
careful [3] 83:2; 372:15; 374:10  
carefully [1] 406:1  
careless [1] 372:17  
carried [2] 148:7; 193:4  
carries [1] 256:19  
carry [6] 239:1; 243:1, 17; 245:19; 250:3;  
418:14  
carrying [2] 238:8; 245:7  
cartoon [1] 17:5  
case [15] 28:9; 33:3; 54:10; 82:20;  
133:15; 185:8; 196:8; 224:10; 226:19;  
233:16; 256:13; 301:1; 314:21; 315:17;  
321:15  
cases [13] 77:15; 83:16; 124:11; 165:18;  
167:11, 12; 175:16; 185:12; 227:16;  
285:4; 302:3; 348:19; 388:6  
categorical [4] 69:10, 17; 149:20; 218:9  
categorically [1] 324:18  
categories [1] 195:9  
category [6] 54:7, 22; 80:12; 154:2;  
160:11; 195:4  
catheter [1] 19:15  
cation [16] 37:9, 11, 16, 18; 38:4, 11, 12;  
39:19, 21; 40:1; 41:20; 88:11; 105:2, 7;  
118:13  
cationian [1] 37:9  
cationic [4] 54:17; 105:7; 108:21; 118:10  
cations [4] 38:7, 18; 67:3; 90:16  
caught [1] 380:16  
causal [1] 121:14  
caused [7] 34:20; 37:21; 41:9; 121:21, 22;  
313:20; 330:21  
caution [1] 6:4  
cautious [1] 169:5  
cells [1] 39:8  
censored [2] 249:10, 15  
Center [1] 8:10  
center [2] 76:6; 298:7  
centers [1] 135:11  
Central [2] 11:12; 82:13  
central [3] 72:16; 298:6; 300:11  
centralized [1] 298:6  
cerebral [1] 251:13  
certainty [1] 346:1  
CG [1] 46:1  
chair [1] 385:13  
Chairman [1] 178:10  
Chairperson [1] 4:4  
chance [10] 51:13; 57:2; 67:9; 78:13;  
84:12, 15; 120:17; 237:5; 238:12; 297:22  
chances [3] 209:9; 244:16; 367:13  
change [24] 48:16; 49:8; 50:22; 63:20;  
65:14; 95:12; 96:13; 106:2; 108:7; 116:10;  
124:5; 138:9; 149:21; 218:9, 13, 18;  
229:3; 289:17; 303:15; 312:11; 338:15,  
16; 362:16; 386:11  
changed [5] 81:6; 106:14; 222:8; 341:3;  
407:18  
changes [14] 50:14; 55:18, 19; 65:19;  
97:8; 102:12; 106:17; 116:14, 15, 16;  
117:9; 177:22; 307:4; 356:20  
changing [2] 57:21; 342:4  
channel [1] 275:12

characteristic [1] 112:9  
 characteristics [8] 34:3; 137:11; 139:17;  
 143:18; 156:8; 159:8; 163:21; 266:20  
 characterization [3] 106:11; 126:10, 11  
 characterize [1] 12:5  
 characterized [2] 75:3; 125:15  
 characterizing [1] 106:21  
 charged [1] 37:13  
 check [5] 304:21; 377:7; 395:7; 396:7;  
 403:18  
 checked [3] 133:15; 226:20; 344:14  
 chemical [1] 329:5  
 chemistry [1] 77:14  
 Chen [3] 417:20; 422:22; 423:6  
 chest [1] 147:22  
 CHF [37] 66:15; 159:9, 13, 19; 160:2;  
 161:22; 162:12, 16; 164:18; 165:14;  
 170:10; 172:19; 180:11; 181:14, 15;  
 182:7; 185:10; 193:2, 3, 7, 14, 16, 22;  
 226:13, 22; 227:4; 280:4, 5, 7, 10, 11, 15,  
 22; 352:2, 3  
 choice [3] 25:8; 273:11; 285:13  
 choices [3] 305:14; 406:9, 11  
 chose [3] 207:20; 246:16; 315:18  
 chronic [31] 11:20; 12:11; 13:11; 17:6, 21;  
 24:10; 25:13, 21; 27:21; 29:21; 30:3;  
 46:16; 62:13; 98:20; 131:6, 9, 18; 134:9;  
 135:3, 6, 12; 142:2; 144:12; 150:4; 152:6;  
 157:9; 179:10; 255:12; 366:2; 390:7;  
 410:21  
 chronically [2] 64:8; 96:19  
 chronicity [1] 18:6  
 Cilostazol [1] 7:2  
 Cimetidine [11] 37:17, 21; 38:20, 21;  
 43:11; 54:18, 21; 90:7, 15; 91:9, 12  
 cimetidine [1] 88:22  
 Cindy [15] 223:2; 315:22; 320:10, 19;  
 322:3; 326:6; 347:20; 350:2; 376:12;  
 382:10; 386:15; 402:2; 411:3; 415:5;  
 419:1  
 circled [1] 168:11  
 circulating [1] 94:17  
 circumstance [1] 106:22  
 circumstances [1] 234:3  
 citing [1] 407:6  
 Citizen [3] 4:10, 12; 6:14  
 claim [3] 170:7; 225:18; 335:11  
 clarification [4] 11:4; 217:20; 225:4; 322:1  
 clarified [1] 222:11  
 clarify [5] 29:17; 112:4; 217:8; 253:3;  
 326:7  
 Class [1] 18:18  
 class [21] 5:9; 7:12; 12:7; 22:7; 123:20;  
 139:21; 162:1; 189:21; 190:4, 10, 14;  
 191:4; 195:4; 224:11; 280:18, 19, 20;  
 324:5; 384:20  
 classes [4] 89:5; 190:2; 194:20; 360:4  
 classical [1] 252:8  
 classification [2] 30:10; 287:11  
 classified [2] 160:12, 15  
 claudication [1] 7:3  
 clear [26] 45:17; 68:14; 124:3, 16, 17;  
 140:15; 150:9; 154:22; 190:15; 191:6;  
 202:10; 221:11; 222:9; 223:22; 243:21;  
 246:3; 254:12; 274:16; 277:19; 342:19;  
 355:7; 359:1; 378:7; 405:17, 19; 406:3  
 clearances [5] 47:5; 117:9; 212:3; 261:1;  
 399:20  
 clinic [2] 329:1; 344:12  
 Clinical [3] 9:8; 11:11, 12  
 clinically [8] 40:8; 105:12; 137:10; 161:19;

168:18; 173:5; 174:13; 335:2  
 clinician [5] 14:13; 202:11; 324:16; 358:8;  
 368:11  
 clinicians [4] 165:9; 298:19; 310:16;  
 331:14  
 clinics [1] 240:4  
 closer [3] 52:8; 65:10; 102:20  
 closest [1] 214:11  
 Clozapine [1] 299:18  
 clozapine [1] 396:15  
 Cococroft [1] 244:4  
 Cococroft-Cault [4] 36:6, 9; 46:2; 76:4  
 code [1] 299:21  
 coefficient [1] 73:5  
 cogent [1] 384:19  
 Cohn [1] 27:6  
 Cokroft-Gault [1] 133:2  
 colleagues [3] 56:11; 64:20; 274:17  
 collect [1] 145:14  
 collected [3] 44:18; 145:17; 148:4  
 collectively [1] 232:5  
 column [3] 39:4; 47:6; 146:9  
 columns [1] 50:20  
 combination [1] 303:16  
 combinations [3] 66:20; 117:17; 118:2  
 combined [7] 142:9, 18; 143:8; 145:2;  
 161:18; 171:3; 285:18  
 combines [1] 211:17  
 combining [1] 215:21  
 comers [1] 274:5  
 comfort [5] 88:12; 111:19; 292:9; 294:10;  
 404:2  
 comfortable [7] 282:11; 342:22; 356:15;  
 395:9, 13, 14  
 comforting [1] 224:13  
 coming [11] 57:15; 69:22; 72:18; 120:6;  
 239:13; 261:4; 272:8; 274:11; 290:1;  
 369:16; 399:18  
 commend [1] 241:21  
 comment [25] 4:6; 10:14; 19:1; 31:15;  
 65:9; 81:21; 95:2; 98:5; 107:19; 190:8;  
 208:19; 214:14; 228:6; 231:20; 235:1;  
 261:3; 262:22; 266:12; 281:1; 303:9, 21;  
 312:18; 337:5; 379:11; 388:3  
 commented [1] 376:16  
 comments [15] 7:17; 9:21; 14:4, 6; 39:11;  
 51:9; 178:21; 179:11; 184:5; 188:16;  
 189:14; 220:10; 301:7; 336:1; 391:9  
 Commission [1] 406:14  
 commitment [1] 297:16  
 commitments [1] 417:13  
 committed [1] 273:14  
 Committee [13] 4:14; 6:21; 8:9; 11:1, 6,  
 15; 32:19; 108:11; 130:16; 153:4; 178:16;  
 298:3; 356:1  
 committee [18] 7:8; 14:1; 121:8; 158:6;  
 160:12; 165:8; 168:20; 210:19; 211:22;  
 212:9; 226:10; 240:20; 286:10; 293:4, 13;  
 294:9; 338:3; 394:9  
 committees [3] 406:12, 15, 16  
 common [7] 14:11, 12, 20; 32:7; 211:4;  
 254:4; 420:13  
 commonest [1] 17:11  
 commonly [13] 12:1; 18:1; 20:18; 27:19;  
 38:17; 114:5; 189:12; 254:1; 301:18;  
 318:9; 419:21; 420:16, 18  
 communicate [1] 300:11  
 community [3] 300:22; 301:16, 17  
 companies [1] 410:11  
 company [15] 10:3; 61:7; 68:10; 77:9;  
 78:1; 126:17; 220:22; 232:15; 233:2;

248:3; 299:13; 311:5; 397:21; 406:22;  
 407:18  
 comparable [8] 94:4; 137:17; 141:15;  
 180:3; 184:9; 189:2; 196:2; 263:15  
 comparative [1] 192:20  
 comparator [4] 135:16; 375:7, 17; 376:1  
 compare [4] 185:2; 191:18; 258:18;  
 316:15  
 Compared [1] 323:22  
 compared [36] 21:7; 27:3; 28:5; 40:14;  
 44:11; 116:11; 125:12; 137:22; 141:18;  
 143:1, 13; 146:17; 147:6, 10; 148:9, 12;  
 150:22; 163:2, 16; 171:9, 18; 173:17;  
 180:8; 182:11; 183:5, 16; 188:21; 189:10;  
 191:22; 202:8; 204:20; 311:11; 323:17;  
 353:6;  
 376:15, 18  
 compares [2] 135:17; 156:1  
 comparing [1] 377:1  
 comparison [9] 138:22; 140:7; 267:2;  
 280:4, 8; 281:13; 417:15, 22; 419:20  
 comparisons [1] 257:9  
 compelling [3] 285:10; 325:3, 6  
 competing [1] 10:3  
 complete [3] 11:3; 297:15, 16  
 completed [3] 43:16, 17; 210:4  
 completely [10] 25:5; 44:14; 56:4, 6; 85:3;  
 124:3; 127:1; 282:22; 323:2; 397:17  
 completing [2] 5:17; 208:4  
 complex [2] 125:14; 126:13  
 compliance [4] 304:14, 16, 19; 306:2  
 complicated [3] 98:14; 178:7; 359:3  
 complications [1] 354:2  
 component [11] 35:19; 40:10, 11; 41:19;  
 74:11; 96:4; 118:9, 11; 161:15; 421:21;  
 423:1  
 composite [4] 15:4; 183:13, 17; 189:19  
 compound [1] 312:14  
 comprised [1] 162:14  
 comprising [2] 153:21; 154:6  
 compromise [1] 391:19  
 compromised [2] 132:16; 174:3  
 computers [1] 77:10  
 concentration [30] 33:12; 34:21; 44:3, 19;  
 49:8; 50:15; 51:20; 56:22; 59:10; 62:6;  
 64:17; 65:3, 7, 14; 68:16, 19; 69:2, 18;  
 70:15; 71:8, 18; 72:11; 78:17; 104:13;  
 117:1; 303:2, 4; 364:5, 9  
 concentrations [23] 34:13; 40:16; 44:10;  
 46:11, 21; 47:7, 8; 49:6, 20; 57:15; 70:4;  
 86:4; 87:7; 88:8; 92:9; 93:6; 94:3, 18;  
 110:10; 115:19; 116:20; 122:21; 282:4  
 concept [1] 394:17  
 concern [26] 54:4; 68:6, 13; 168:20;  
 170:18; 177:4; 183:8; 188:5; 223:11, 12;  
 232:13; 264:5; 293:5, 12; 294:6; 315:5;  
 316:15; 318:7; 322:19; 354:13; 357:8;  
 374:8; 387:2, 17; 412:13  
 concerned [20] 4:17; 7:1; 29:21; 52:20;  
 80:20; 86:1; 128:3; 178:1; 223:12; 228:16,  
 17; 256:17; 258:5; 311:19; 313:16;  
 372:20; 382:15; 397:7; 398:3; 402:18  
 concerning [5] 4:15; 165:8; 322:16  
 concerns [14] 5:3, 13; 58:2; 80:5; 191:8;  
 232:19; 296:18, 22; 306:20; 335:19;  
 358:18; 373:14; 390:5; 419:10  
 concert [3] 275:12, 13; 320:19  
 conclude [6] 33:21; 103:18; 174:1; 185:1;  
 299:12; 302:11  
 concluded [2] 353:13; 423:11  
 concludes [2] 10:15; 51:9

concluding [2] 173:21; 337:18  
 conclusion [9] 12:9; 21:8; 221:20; 225:12;  
 232:5; 246:15; 299:10; 302:9, 10  
 conclusions [5] 72:18; 250:12; 291:3;  
 37:1; 353:18  
 concomitant [20] 38:15; 43:8, 20; 66:6;  
 108:9; 109:20; 110:1; 111:4; 137:13, 15,  
 16; 175:9; 176:15, 18; 177:17, 19, 21;  
 267:1; 272:17  
 condition [5] 7:4; 386:7, 8, 9; 418:3  
 conditions [5] 250:16; 300:21; 383:17, 18;  
 401:10  
 conduct [1] 9:15  
 conducted [8] 9:13; 33:5; 87:1; 135:11;  
 157:1; 246:21; 253:6; 298:17  
 conduction [3] 6:10; 274:21; 275:8  
 confidence [14] 156:17; 158:3; 160:4;  
 164:20; 186:12, 14, 15; 242:5; 261:5;  
 262:18; 263:2; 264:3; 284:22; 371:3  
 confident [4] 29:11; 63:18; 340:13; 342:16  
 confirmatory [2] 134:16; 237:16  
 confirmed [7] 37:1; 41:5; 49:12; 138:4;  
 142:5; 145:1; 149:21  
 confirms [1] 21:1  
 conflict [3] 8:1, 4, 12  
 confounded [1] 177:9  
 confused [4] 56:18; 104:10; 231:7; 338:1  
 confusing [1] 358:22  
 confusion [4] 258:12; 274:15; 276:11;  
 344:16  
 congestive [13] 16:11; 20:21; 25:2; 132:7;  
 159:5; 181:10; 182:10; 183:6; 192:19;  
 193:5, 13; 194:22  
 conglomerate [1] 236:14  
 conscience [1] 314:12  
 consecutive [1] 83:17  
 consequence [1] 184:13  
 consequences [8] 14:8; 16:7; 125:18;  
 169:1; 174:10; 196:9; 406:10; 412:21  
 conservative [3] 218:19; 282:10; 419:6  
 consider [12] 34:16; 162:9; 208:14;  
 232:13; 252:10; 255:21; 262:10; 298:3;  
 338:14; 357:19, 20; 421:8  
 considerable [1] 351:16  
 considerably [2] 257:10; 378:1  
 consideration [3] 37:12; 50:8; 284:18  
 considerations [3] 46:8; 356:17, 21  
 considered [13] 38:18; 76:15; 79:17;  
 128:5; 136:5; 140:12; 147:15; 249:10, 11,  
 14; 285:21; 352:17; 402:5  
 considering [4] 42:11; 79:1; 390:20;  
 401:13  
 consist [2] 154:2; 322:12  
 consistency [1] 243:2  
 Consistent [2] 45:13; 132:14  
 consistent [13] 36:17, 19, 39:21; 79:13;  
 126:3; 242:4, 9; 246:11; 261:8; 321:14;  
 341:12; 349:3; 365:17  
 consistently [2] 110:14; 281:10  
 consists [1] 79:16  
 constellation [1] 267:8  
 constitute [2] 19:5; 196:14  
 construct [2] 110:19; 339:20  
 consultant [2] 51:15; 283:6  
 consultants [1] 197:9  
 consumed [1] 15:20  
 consumes [1] 15:17  
 consuming [1] 15:22  
 contained [1] 167:9  
 contains [1] 146:9  
 contemplating [1] 328:1

context [3] 254:11; 377:19; 404:3  
 contingent [1] 297:4  
 continue [9] 78:2; 200:12; 204:16; 314:1;  
 356:6; 412:18; 413:20; 414:15, 20  
 continued [6] 46:1; 206:14; 270:21;  
 357:12; 415:14; 416:5  
 continuing [2] 7:2; 29:2  
 continuous [5] 132:13; 360:15; 364:4, 5, 9  
 continuously [2] 82:16; 84:2  
 contraceptives [8] 91:20; 92:6, 8, 13, 18,  
 19; 93:1  
 contradict [1] 259:16  
 contraindicate [1] 99:22  
 contraindicated [1] 195:6  
 contraindications [1] 310:13  
 contrast [3] 44:15; 139:22; 191:3  
 contribute [2] 40:19; 385:21  
 contributed [1] 175:14  
 contributes [1] 155:20  
 contribution [2] 16:4, 10  
 control [34] 16:16; 17:3; 18:11; 24:14;  
 26:8; 27:3; 99:3; 127:5; 135:16; 144:14,  
 17; 151:20; 152:8, 18; 155:5; 188:21;  
 189:2; 272:10; 273:2, 6, 7, 8, 15; 274:9,  
 13; 275:6, 8, 11; 276:18; 285:11; 308:19;  
 315:15; 320:7; 387:20  
 controlled [13] 12:13, 18; 102:7; 131:20;  
 156:3; 157:3; 158:15; 166:10; 169:9, 14;  
 184:8, 18; 271:11  
 controlling [2] 24:15; 270:19  
 controls [3] 93:9; 95:4; 189:6  
 conundrum [1] 415:21  
 conventional [2] 28:19; 409:21  
 conventionally [1] 39:16  
 conversation [1] 174:16  
 converse [1] 92:7  
 conversion [45] 11:18; 19:21; 24:16;  
 25:17; 28:12, 17; 49:1; 130:19; 131:5;  
 150:2, 9, 13, 16, 20; 151:7, 20; 152:3, 20;  
 179:9, 20; 183:3; 194:11; 195:22; 200:22;  
 248:19; 320:13; 321:18; 323:8, 19;  
 324:10; 326:9, 12, 16, 20; 330:21; 331:2;  
 333:8, 16; 340:1; 360:18; 381:18; 382:3,  
 5; 389:20; 412:1  
 convert [18] 98:10; 136:7, 10; 138:5;  
 150:6; 151:5; 200:18; 201:1; 202:18;  
 203:3; 229:19; 247:15, 18; 327:6; 328:2;  
 332:6; 361:6  
 converted [14] 28:7; 48:20; 135:20;  
 150:22; 151:4, 14; 179:12; 180:18; 202:7;  
 205:2; 225:1; 332:2; 361:15; 410:21  
 converters [1] 180:22  
 convertible [1] 30:13  
 converting [12] 141:12; 150:15; 151:9;  
 194:5; 248:2, 7; 264:18; 265:5, 6; 319:22;  
 323:16; 354:9  
 converters [2] 181:2, 5  
 converts [1] 266:1  
 convinced [11] 242:13; 316:20; 328:20;  
 329:3; 332:12; 333:6; 334:12; 336:13;  
 345:19; 361:8; 400:5  
 convinces [1] 400:3  
 convincing [2] 239:11; 363:18  
 coordinator [1] 373:11  
 copy [2] 8:16; 288:20  
 core [10] 119:6; 203:11; 216:2; 226:7;  
 229:2; 258:22; 262:2; 264:10; 272:13  
 cornerstone [1] 196:14  
 cornerstones [1] 184:14  
 corollary [2] 249:15; 401:5  
 coronary [1] 190:12

corporate [1] 10:2  
 corrected [6] 5:22; 83:3; 127:8; 215:12;  
 246:22; 381:1  
 correction [1] 82:6  
 correctly [4] 173:18; 243:4; 323:7; 405:8  
 correlated [1] 152:15  
 correlates [1] 50:15  
 correlation [3] 50:16; 73:4; 279:13  
 corresponding [1] 239:16  
 corroborated [1] 144:16  
 Cosmetic [1] 339:3  
 cost [3] 15:18; 16:1; 340:4  
 costs [1] 21:11  
 coumadin [1] 29:7  
 counsel [1] 392:1  
 count [2] 255:15; 338:4  
 counted [2] 168:10; 222:17  
 counter [1] 99:16  
 counting [1] 318:19  
 countries [1] 25:9  
 country [6] 56:13; 58:2; 60:6; 230:10;  
 237:7, 8  
 couple [16] 51:5; 55:4; 88:20; 173:22;  
 177:13; 198:13; 207:18; 237:9; 239:4;  
 245:10; 250:9; 275:18; 286:21; 292:5;  
 312:10; 404:12  
 course [25] 56:22; 63:7; 64:2; 65:20;  
 66:13; 72:19; 104:20; 109:11; 137:12;  
 154:18; 187:11; 205:14; 208:8; 222:9;  
 226:21; 268:8; 276:14; 284:7, 11; 287:9;  
 292:13; 360:11; 368:6; 399:16; 407:19  
 covered [1] 107:22  
 covers [1] 133:5  
 CP [1] 69:8  
 CQT [1] 268:17  
 crack [2] 312:1; 362:22  
 Craig [23] 13:17, 18; 32:15, 20; 51:17;  
 58:1; 67:19; 78:3; 84:20; 95:3; 109:5;  
 110:22; 112:3; 113:3; 120:14; 153:1;  
 216:18; 223:8; 225:20; 283:14; 286:20;  
 313:5; 400:11  
 crazy [2] 309:17  
 create [3] 318:2, 5, 10  
 created [1] 367:9  
 Creatinine [4] 37:19; 45:19; 46:1; 47:5  
 creation [1] 230:5  
 credible [2] 337:22; 339:1  
 creeping [1] 258:4  
 criteria [3] 199:15; 218:19; 252:6  
 critical [8] 27:11; 51:21; 161:15; 184:14;  
 196:14; 317:8; 365:19; 419:16  
 critically [1] 282:5  
 crossed [1] 82:22  
 crowd [1] 198:6  
 crux [1] 314:3  
 crying [1] 195:10  
 cuff [1] 59:14  
 curative [1] 19:15  
 current [11] 10:13; 13:10; 14:10; 21:13;  
 65:17; 83:17; 97:22; 195:18; 239:11;  
 247:8; 380:22  
 currently [9] 15:15; 19:20; 20:1; 43:18;  
 179:7; 196:3, 21; 315:20; 374:14  
 curve [20] 71:15; 72:8; 75:2; 95:4; 96:13;  
 138:7; 140:14, 15; 172:7; 192:22; 203:10;  
 206:20; 207:5, 13; 209:3; 215:10; 264:16,  
 17; 265:1; 359:20  
 curves [14] 94:7; 137:20; 170:6; 181:13;  
 191:21; 193:1; 203:13; 204:3, 4, 12;  
 208:20; 248:13; 288:4; 375:10  
 cut [3] 59:6; 96:7; 102:5

cuts [1] 108:8  
cutting [1] 56:2  
cycle [1] 97:1  
CYP [1] 40:20  
CYP3A4 [10] 34:9; 39:18; 40:21, 22; 41:2, 7; 42:2, 12, 17; 52:4

- D -

D'AGOSTINO [38] 237:7; 242:18; 244:12; 245:1, 6, 14, 17; 246:6, 10, 17; 247:12; 249:6, 18, 21; 250:3, 13; 251:4, 9, 15, 19; 252:17; 253:18; 254:10; 256:10; 257:12, 20; 259:11; 260:11; 261:10; 321:12; 327:5; 332:15; 341:17; 358:14; 372:18; 378:22; 384:2; 390:3  
D'Agostino [3] 8:16; 198:19; 250:22  
D-Sotalol [2] 191:4, 21  
D.C. [1] 4:11  
damn [1] 394:3  
Dan [1] 8:20  
dangerous [4] 124:18; 125:1; 336:16; 346:4  
Danish [1] 298:4  
Data [1] 48:18  
date [1] 189:3  
daunting [1] 418:2  
day [50] 29:19; 46:18; 47:6; 48:11; 54:1; 57:18; 61:12, 20; 62:3, 12; 72:19; 75:20; 77:10; 93:10; 100:6, 7, 8, 16, 21; 102:14; 121:18; 123:13; 124:4; 136:6, 8; 150:19; 153:14; 199:1, 3, 4; 210:15; 211:10; 229:5, 7; 234:14; 247:10; 259:20, 22; 260:6; 291:18; 307:2; 318:8; 340:3; 348:17; 356:18; 402:6; 413:9; 419:10  
day-to-day [1] 332:16  
days [35] 15:20; 16:1; 45:14; 49:15; 58:8, 13, 22; 59:3, 9; 62:7; 84:2; 99:9; 100:7; 102:16; 121:15; 123:11, 19; 135:22; 137:10; 166:14, 18, 22; 169:3; 198:13; 199:8; 201:10; 240:13; 250:9; 297:9; 299:22; 338:14; 367:2, 3; 402:9; 415:14  
DC [3] 136:9; 151:6; 201:15  
de [10] 13:1; 122:7; 165:9; 173:17; 175:16; 184:3; 185:6; 196:8; 278:9; 282:2  
dead [1] 366:11  
deal [9] 15:18; 112:2; 130:7; 175:6; 191:14; 326:2; 359:16; 361:15; 415:19  
dealing [4] 343:20; 348:18; 370:22; 372:1  
deals [1] 207:16  
dealt [1] 360:13  
death [16] 5:8; 16:14, 17; 160:7, 10, 14, 16; 165:4, 5; 183:14; 286:17; 287:14; 288:5, 10; 289:7; 314:16  
deaths [32] 6:18; 157:22; 160:5, 8, 11; 161:18; 164:6; 167:13; 284:15; 285:5; 286:14; 287:1, 4, 10, 17; 288:3, 10, 22; 290:11, 14, 20; 317:7, 11, 13, 16; 318:21; 366:6, 8, 15; 371:12; 407:7  
debatable [2] 81:17; 329:22  
debate [3] 121:18; 123:14; 330:3  
decide [5] 7:8; 260:8; 292:21; 355:2; 420:14  
deciding [1] 340:3  
decision [6] 213:16, 19, 20; 309:2; 355:16; 365:12  
decisions [1] 309:3  
declare [1] 273:12  
decline [1] 74:14  
declines [3] 73:15, 17; 74:1  
decompensate [1] 331:19

decompress [1] 326:3  
decrease [8] 34:17; 38:15, 22; 42:8; 63:7; 96:6, 10; 105:11  
decreased [13] 45:19; 50:13; 58:16; 63:11; 70:12; 79:11; 102:22; 152:15; 155:17; 271:20, 21; 370:2; 379:18  
decreases [2] 41:12; 42:4  
decreasing [5] 63:18; 73:16, 17; 74:15; 113:20  
decytochrome [1] 421:1  
deeply [2] 4:16; 6:15  
defend [1] 128:1  
deferral [1] 333:21  
defibrillators [1] 338:15  
deficiency [1] 75:4  
definable [1] 365:8  
define [8] 36:1; 53:9; 71:7; 105:10, 13; 314:15; 348:20; 393:3  
defined [10] 29:10; 59:7; 82:18; 131:10; 314:6; 345:11; 349:1; 350:1; 371:1  
defining [1] 33:9  
definite [1] 60:9  
definitely [6] 167:22; 171:13; 278:8; 300:21; 321:19; 342:12  
definition [3] 31:4; 100:1; 394:7  
definitions [1] 31:18  
definitive [9] 87:4; 95:1; 106:13; 120:12; 190:15; 225:6; 310:19; 338:14; 351:1  
definitively [4] 89:8; 166:22; 191:15; 378:18  
degree [10] 12:6; 35:22; 42:13; 53:11; 241:14; 289:15; 310:2; 371:2; 404:1; 410:13  
degrees [1] 147:9  
delayed [1] 34:14  
delays [1] 123:21  
delighted [1] 274:15  
delineates [1] 17:5  
delusional [1] 149:7  
demographic [1] 159:8  
demographics [2] 43:20; 109:20  
demonstrate [5] 142:19; 152:19; 330:7; 331:3; 332:22  
demonstrated [8] 43:5; 47:20; 142:3; 143:3; 144:13; 145:4; 152:12; 330:9  
demonstrates [4] 140:22; 149:3; 151:16; 224:22  
demonstrating [2] 171:17; 331:7  
demonstration [1] 191:6  
denied [1] 4:16  
Denmark [4] 176:2, 3; 281:4; 298:17  
denominator [1] 290:17  
denoting [1] 353:20  
depend [5] 56:10; 118:7, 16; 370:6, 7  
dependence [1] 45:17  
dependent [2] 118:16; 210:22  
depending [3] 83:18; 202:15; 277:5  
depends [8] 76:9; 81:9; 105:7, 10, 13; 107:1; 339:19; 354:22  
depth [1] 297:22  
derivation [1] 33:17  
derived [4] 23:19; 63:9; 142:17; 154:15  
des [1] 166:12  
describe [4] 109:7; 370:9; 412:15; 416:6  
described [5] 62:8; 108:18; 157:17; 298:5; 394:6  
describing [1] 412:12  
description [1] 391:12  
deserve [1] 234:22  
design [11] 35:15; 134:15; 135:21; 139:8, 9; 142:12; 147:18; 225:16; 248:18; 411:7

designed [11] 44:12; 92:5; 94:21; 135:4; 159:1; 201:14; 209:21; 243:4; 321:2; 345:2; 346:14  
desirable [1] 314:17  
desired [1] 389:20  
Despite [2] 4:21; 49:22  
despite [3] 48:21; 111:4; 149:6  
detach [1] 122:18  
detail [7] 84:20; 88:16; 141:13; 146:4; 158:11; 167:1; 207:17  
detailed [6] 66:4; 75:5; 127:19; 184:4; 215:16; 216:1  
details [1] 155:8  
detected [2] 343:4; 344:11  
deterioration [1] 360:12  
determinant [1] 46:6  
determinants [2] 33:8, 15  
determine [1] 396:11  
determined [5] 8:9; 76:3; 143:16, 19; 194:9  
devastated [1] 392:19  
devastating [1] 391:18  
develop [4] 76:18; 330:20; 360:11, 12  
developed [6] 10:3; 166:11; 215:20; 299:8; 404:2; 423:4  
developing [4] 167:15; 265:15; 307:8; 330:18  
development [7] 12:3; 16:11; 133:22; 172:8; 222:9; 242:9; 374:2  
deviant [1] 119:14  
devoted [1] 98:4  
dexfen [1] 6:19  
DIA [1] 239:13  
diagnosed [1] 23:13  
diagnoses [1] 15:21  
diagnosis [3] 16:4, 5; 122:4  
dial [2] 59:21; 60:10  
dialogue [2] 270:3; 297:14  
diarrhea [2] 65:17; 334:16  
dice [2] 81:10; 285:8  
die [3] 166:22; 291:10; 313:7  
died [6] 166:15; 167:4, 7; 291:9; 296:1; 366:12  
differ [4] 159:3; 202:15; 238:6; 242:15  
difference [34] 44:14; 95:19; 112:19; 140:22; 141:8, 19; 147:14; 150:18; 151:8; 156:15; 159:22; 162:3; 163:8; 180:15; 181:16; 192:16; 202:5; 244:15; 247:20, 22; 259:9, 18; 260:2; 278:14; 280:12; 291:22; 304:16; 310:10; 316:20; 333:10; 345:7; 363:19; 373:10; 393:17  
Differences [1] 138:1  
differences [23] 17:6; 44:13, 15, 16, 19; 95:15; 137:11; 143:17; 149:8; 156:9; 157:13; 162:6; 164:1; 169:17, 18; 174:13; 185:3; 194:6, 8; 224:4; 247:18; 354:10; 367:20  
differential [2] 22:9; 23:1  
differentiate [3] 66:17; 394:5; 399:9  
differently [6] 292:14; 294:1, 4; 308:17; 333:18  
difficult [21] 6:11; 14:16; 18:5; 25:14; 49:19; 69:5, 11; 79:15; 98:17; 186:12; 267:12; 309:2; 317:5, 12, 14; 335:18; 348:19; 349:8; 368:9; 387:5; 397:2  
difficulties [1] 306:21  
difficulty [1] 52:1  
DIG [1] 277:10  
Dig [26] 272:6; 274:6, 9, 20; 275:6, 10; 276:5, 11, 13, 17, 21; 283:13; 284:11, 12,



- 14; 285:1, 11; 286:1, 7; 301:8, 15, 18;  
302:1; 303:10, 16  
dig [1] 382:21  
Digoxin [17] 86:12, 13; 101:19; 111:2, 4;  
14:21; 127:1, 2; 137:13; 140:1; 175:11;  
77:16; 178:5; 272:18; 284:2, 3; 311:15  
Diltiazem [14] 80:8, 11, 20; 99:3, 11, 12;  
101:12, 14, 18, 21; 108:2; 177:12, 13  
diltiazem [1] 80:7  
diminished [4] 18:2; 27:19; 103:17; 310:8  
direct [4] 49:5; 66:12; 306:4; 316:7  
directed [2] 17:3, 4  
direction [3] 63:3; 325:5; 387:13  
directionality [1] 325:5  
directive [1] 409:17  
disabled [3] 388:19, 21; 389:1  
disadvantage [3] 126:14; 313:3, 4  
disagree [9] 223:19; 236:18; 307:13;  
314:2; 324:8; 345:10; 348:1; 392:16;  
405:18  
disagreed [1] 345:14  
disagreeing [3] 227:9; 363:15; 364:17  
disagreement [1] 344:16  
disappointing [1] 224:1  
disaster [2] 374:4, 6  
disastrous [1] 380:9  
discharge [3] 311:12; 316:17; 402:8  
discharged [1] 97:16  
disclose [1] 9:1  
disclosed [1] 9:4  
discomfort [2] 357:12; 417:5  
discomforted [1] 346:7  
discontinuation [6] 155:7, 11, 12; 169:19;  
219:1; 376:17  
discontinuities [5] 161:9; 205:9, 13;  
206:5; 208:7  
discontinue [3] 209:19; 369:2; 411:8  
discontinued [15] 56:4; 136:11; 167:16;  
183:21; 205:5, 22; 206:7, 13, 18; 208:10;  
219:3; 270:20; 280:1; 377:6; 379:18  
discontinuing [2] 56:7; 63:19  
discontinuity [1] 319:1  
discontinuous [1] 364:14  
discover [1] 359:19  
discovered [1] 359:14  
discovery [1] 359:17  
discrepancy [1] 242:11  
discrete [2] 17:14, 20  
discuss [12] 32:15; 36:4; 46:8; 61:10;  
135:2; 142:6; 150:2; 237:3; 239:10;  
297:22; 319:6; 334:3  
discussed [16] 31:19; 41:18; 84:20;  
130:12; 131:22; 141:13; 142:21; 164:10;  
165:13; 170:14; 178:8; 190:8; 237:19;  
261:21; 284:9; 420:10  
discussing [6] 131:16; 198:13; 261:20;  
262:4; 283:7; 413:9  
discussion [41] 11:2; 17:2; 24:13; 30:15;  
19; 51:18, 22; 61:18; 72:16; 84:21;  
104:11; 168:19; 174:17; 184:4; 197:9;  
220:12; 222:7; 232:9; 236:19; 239:6;  
253:11; 254:18; 260:12; 272:7; 276:20;  
307:9; 313:11; 314:3; 316:13; 319:14;  
333:13; 356:5;  
359:4; 374:17; 384:12, 15; 385:10; 392:5;  
6; 408:4; 417:11  
discussions [8] 10:5; 13:9; 34:1; 262:1;  
270:2; 307:15; 374:21; 393:2  
diseases [1] 267:1  
disfunction [1] 385:7  
dismiss [2] 87:10; 211:22  
Disopyramide [2] 180:1; 184:22  
disopyramide [1] 399:1  
disorders [1] 253:13  
dispensed [1] 298:10  
dispensing [1] 396:17  
display [1] 97:7  
displaying [1] 181:13  
disposition [2] 33:8; 36:20  
disseminated [1] 9:14  
dissertation [1] 153:14  
distant [1] 251:13  
distinction [1] 17:7  
distinguish [2] 6:12; 115:17  
distributed [4] 32:5, 6; 227:1, 2  
distribution [8] 15:6, 7, 8; 45:7; 80:1;  
95:12; 271:1, 275:15  
distributions [1] 15:5  
disturbance [2] 82:19; 252:3  
disturbances [1] 4:19  
diuretic [2] 66:20; 112:7  
diuretics [13] 65:17; 66:7, 16, 18, 20;  
67:1; 112:5, 9; 114:11; 137:14; 140:2;  
168:2; 334:15  
divide [2] 240:4, 5  
dizziness [1] 17:15  
doc [1] 325:19  
doctor [2] 230:10; 302:16  
doctors [15] 78:7; 176:5; 230:12; 282:11,  
12; 284:1; 369:1; 372:8; 397:12; 398:8;  
399:3; 405:7, 20; 412:8  
document [22] 107:21; 132:3; 134:2;  
154:19; 155:8; 156:14; 157:19; 158:11;  
164:11; 169:11; 172:1; 174:18, 22;  
175:10; 207:15, 16; 208:3; 215:7; 216:5;  
255:4; 284:8; 285:16  
documentation [1] 393:9  
documented [7] 136:1; 168:7; 332:4;  
343:5; 366:6, 7; 421:15  
documents [2] 174:20; 237:8  
doesn't [41] 60:15; 94:9; 97:22; 104:6;  
111:13; 122:16; 129:12; 166:19; 186:22;  
206:2, 4; 223:9, 15, 21; 225:6; 230:14, 15;  
235:11, 12; 236:4; 238:2, 11; 241:2;  
252:12; 254:9; 259:15; 261:9; 263:12;  
300:4; 313:10, 22; 316:22; 340:19; 345:6;  
350:19; 364:5; 367:3; 378:6; 382:6, 8;  
394:4  
doest [1] 231:11  
dollars [1] 16:2  
domain [1] 103:21  
dominant [3] 23:2; 35:19; 41:19  
Don [2] 228:11; 279:8  
dosage [12] 35:11, 16; 46:15; 155:6, 14,  
17; 160:21; 161:2, 13; 165:1; 184:12;  
265:20  
dosed [11] 46:15; 54:13; 134:5; 152:10;  
216:9, 14; 220:4; 229:18; 260:16; 294:15;  
307:4  
Doses [1] 165:19  
doses [32] 45:12, 18; 46:5, 19; 62:15;  
99:5; 118:16; 122:21; 134:12; 136:18, 20;  
139:15; 155:2; 210:8; 220:1; 228:7, 15;  
229:4; 243:6, 9; 260:2; 262:9; 265:11;  
275:10, 22; 276:16; 297:9; 312:10; 323:8;  
372:10, 17; 375:13  
dosing [43] 33:18; 45:21; 47:3, 9, 14;  
49:15; 50:2; 55:22; 57:17; 60:11, 18;  
133:21; 143:6; 155:4; 158:19; 168:22;  
169:5; 174:10; 218:9, 10; 244:2; 246:4,  
16; 262:6, 12, 13; 263:7; 294:7, 11; 297:7;  
322:12; 357:3, 20; 358:6, 7; 366:4;  
370:10;  
377:16; 397:19; 399:4, 22; 404:3; 421:12  
double [7] 131:19; 135:15; 144:13;  
151:19; 158:16; 168:10; 271:22  
doubled [1] 359:15  
doubles [1] 127:2  
doubling [1] 373:17  
doubt [3] 124:15; 125:4; 362:17  
down-titrate [2] 211:9; 279:21  
downward [6] 132:16; 136:18; 148:11;  
266:6; 358:9, 20  
draft [1] 75:11  
dramatic [2] 112:13; 367:20  
draw [8] 82:20; 88:6; 207:15; 291:2;  
292:9; 306:18; 311:20; 336:17  
drawing [1] 331:18  
drawn [5] 110:10, 14, 16; 180:11; 184:20  
dreamed [1] 127:13  
drew [1] 353:18  
drive [4] 102:8; 270:5; 400:16; 406:1  
driven [5] 112:7; 208:8; 270:1; 291:6;  
343:15  
drivers [1] 290:3  
driving [2] 220:19; 309:16  
drop [7] 47:10; 138:7; 140:13; 183:10;  
203:7; 213:13; 316:4  
dropped [7] 80:16; 104:13; 148:6; 209:13;  
227:21; 249:9; 280:1  
dropping [1] 249:7  
drops [1] 74:10  
Drs [2] 8:20; 178:15  
Drug [3] 8:10; 339:3; 358:16  
drug-drug [1] 86:1  
Drugs [1] 338:11  
druthers [1] 398:7  
due [15] 6:3; 34:22; 35:2; 38:1; 46:19;  
56:4; 114:17; 143:16; 155:11, 12; 167:13;  
195:16; 206:7; 376:17; 387:1  
Duke [3] 9:8; 145:19; 157:1  
dumb [1] 328:18  
dummy [1] 271:22  
dump [2] 87:14; 115:15  
duration [6] 22:19; 50:11; 135:13; 137:9;  
235:8; 249:3  
dwell [1] 253:22  
dying [2] 281:8; 366:10  
dysfunction [20] 24:4; 154:8; 159:7;  
161:7; 192:3, 4, 8, 16; 193:5; 213:18;  
315:16; 348:8; 349:5; 350:6, 14; 351:4;  
357:2, 7; 358:10; 390:1  
dysfunctional [1] 98:22  
dyspnea [4] 17:15; 18:1; 27:20; 310:9

## - E -

- early [9] 5:10; 103:17; 144:22; 159:6;  
162:10; 211:8; 219:8; 226:17; 253:16  
easily [2] 291:4; 333:2  
easy [11] 71:18; 72:8; 98:11, 16; 332:22;  
358:10; 389:5; 397:2; 400:20; 403:16, 19  
EC50 [2] 71:4; 72:13  
ECG [6] 303:15; 343:14; 344:8, 11;  
345:19; 402:5  
ECGs [3] 273:15; 311:10; 368:18  
echo [1] 115:4  
echocardiographic [1] 352:12  
edge [1] 76:20  
educate [2] 77:2; 398:8  
education [2] 76:16; 297:20  
educational [4] 77:6; 78:2; 397:20; 404:19  
effected [1] 343:19

- effective [16] 12:14; 25:4; 70:3; 77:6;  
 138:12; 151:18; 180:6; 195:22; 198:7;  
 201:15; 265:11, 17; 354:8; 378:6; 380:12;  
 404:21  
 effectively [3] 7:5; 9:13; 266:2  
 effectiveness [5] 11:18; 124:2, 22; 300:17;  
 409:2  
 effects [33] 5:5; 39:10; 40:1; 42:1; 47:16;  
 17; 50:18; 55:5, 10; 62:14; 81:11; 103:16;  
 109:16; 110:2; 113:6; 114:14; 147:13;  
 148:19; 184:1; 191:11; 194:12; 314:18;  
 332:8; 340:8; 346:17; 347:16; 369:21;  
 376:7; 378:1, 14; 381:5; 421:2, 18  
 efficacious [2] 152:6; 382:15  
 Efficacy [2] 152:12; 203:11  
 effort [6] 18:2; 27:19; 198:4; 310:8;  
 397:20; 404:9  
 efforts [3] 77:6; 78:3; 407:1  
 eight [3] 146:1; 147:4, 8  
 ejection [7] 48:8, 16; 55:6, 15, 21; 158:13;  
 336:20  
 EKG [5] 132:22; 199:13; 268:9; 278:17, 21  
 EKGs [4] 83:18, 19; 268:20; 269:2  
 elaborate [1] 382:13  
 elderly [11] 78:17; 79:9, 10, 16, 18; 80:2;  
 93:15; 117:19; 167:22; 171:19; 298:11  
 elected [1] 231:10  
 electrical [5] 202:13, 19; 203:2; 320:15;  
 329:5  
 electrically [3] 179:13; 201:11; 248:22  
 electricity [1] 200:8  
 electrocardial [1] 12:15  
 electrocardiogram [2] 136:2; 356:20  
 electrocardiographic [1] 132:13  
 electrocardioversions [1] 200:3  
 electronic [1] 78:6  
 electrophysiologic [6] 6:9; 14:15; 274:16;  
 281:22; 311:7, 8  
 electrophysiologists [1] 176:8  
 electrophysiology [2] 312:16; 328:22  
 elegant [1] 126:17  
 elegantly [2] 67:21; 178:8  
 element [1] 397:11  
 elements [1] 239:15  
 eleven [1] 317:10  
 eliminated [3] 35:7; 168:22; 214:8  
 eliminating [1] 174:7  
 elimination [8] 35:8, 20; 40:11, 14; 73:9,  
 10; 75:10; 96:4  
 embolism [2] 28:11; 268:4  
 emphasis [2] 24:15; 210:13  
 emphasize [6] 16:19; 19:12; 185:8;  
 187:20; 193:9; 352:15  
 emphasized [2] 73:8; 185:7  
 emphasizes [2] 93:22; 194:17  
 emphasizing [2] 154:22; 159:20  
 empiric [1] 232:5  
 empirical [2] 231:2; 361:9  
 empirically [1] 231:4  
 employed [3] 18:19; 19:4; 20:16  
 employer [1] 9:8  
 emptying [1] 31:5  
 emulate [1] 173:8  
 enact [1] 408:16  
 encounter [1] 372:7  
 encouragement [1] 369:17  
 encouraging [2] 190:5; 419:8  
 end [30] 13:9; 23:21; 47:8; 53:22; 61:12,  
 19; 65:11; 82:17, 18, 22; 87:14; 93:22;  
 95:16; 128:7; 130:12; 148:4; 187:9, 12;  
 190:20; 203:20; 204:1; 207:3, 20; 257:4;  
 340:2; 343:6, 18; 352:21; 365:21; 367:18  
 endpoint [21] 111:22; 134:20; 137:19;  
 138:19; 144:14; 145:9; 150:20; 158:20;  
 159:16; 181:9; 241:4; 252:9; 258:13, 20;  
 321:3; 325:8; 335:20; 336:7; 338:2; 339:2;  
 343:16  
 endpoints [8] 131:2; 145:6; 313:17; 336:2;  
 338:4, 10, 13; 363:21  
 ends [3] 86:17, 20; 109:1  
 enhance [1] 201:6  
 enlargement [1] 352:10  
 enormous [5] 15:18; 21:9; 188:13;  
 289:11; 303:5  
 enroll [2] 281:4, 11  
 enrolled [6] 43:17; 131:20; 200:2, 7, 22;  
 308:12  
 ensure [3] 9:12; 396:20; 405:20  
 enter [1] 337:11  
 entered [11] 150:3; 164:9; 166:1; 193:20;  
 194:1; 202:3; 205:21; 207:7; 247:1; 272:4;  
 309:10  
 entering [1] 363:7  
 enthusiasm [2] 243:5; 325:12  
 entirety [1] 246:20  
 entity [1] 122:16  
 Entry [1] 132:2  
 entry [4] 180:12; 182:6, 19; 199:15  
 enumerated [1] 105:3  
 environment [2] 13:10; 255:15  
 envision [2] 308:11; 372:9  
 enzyme [6] 41:1, 4; 52:13, 18; 53:5; 54:8  
 enzymes [1] 40:21  
 epidemiological [1] 66:10  
 epidemiology [1] 14:8  
 episode [1] 122:9  
 episodes [5] 5:18; 17:14; 23:15; 168:14;  
 319:22  
 Epselom [1] 242:1  
 equal [9] 13:1; 93:21; 158:13; 240:9;  
 261:12, 13, 14  
 equally [4] 32:9; 227:1, 2; 319:2  
 equation [8] 36:7, 9; 46:2; 76:4, 18;  
 116:21; 244:4; 334:4  
 equations [1] 73:6  
 equivalent [8] 6:6; 35:1; 132:17; 137:2;  
 158:13; 240:7, 17; 294:14  
 era [1] 379:13  
 erythromycin [1] 103:6  
 escaped [1] 66:2  
 essence [1] 202:2  
 essential [2] 121:4; 300:12  
 Essentially [1] 207:14  
 essentially [7] 92:17; 109:18; 117:18;  
 173:8; 207:18; 272:9; 319:12  
 established [5] 145:18; 146:21; 190:9;  
 199:12; 226:11  
 establishing [1] 154:11  
 estimate [22] 52:5, 7; 70:2; 75:15; 76:5;  
 77:3, 22; 109:15, 16; 139:3; 156:5, 19;  
 163:19; 171:16; 173:14; 203:19; 242:17;  
 263:20; 284:22; 304:10; 351:1; 367:8  
 estimated [10] 36:6, 8; 46:3; 73:3; 76:3, 8;  
 87:21; 138:21; 143:14; 244:3  
 estimates [13] 137:19; 139:7; 157:16, 18;  
 158:2; 161:22; 162:15; 164:19; 173:16;  
 186:13; 220:7; 267:15; 284:21  
 estimation [3] 242:16; 274:8; 344:17  
 etcetera [3] 118:18; 347:1; 386:21  
 Ethambutol [1] 90:20  
 ethical [1] 408:9  
 Ethinylestradiol [1] 94:17  
 ethinylestradiol [1] 94:13  
 Europe [1] 25:8  
 European [1] 190:18  
 evaluate [3] 9:20; 209:20; 365:18  
 evaluated [5] 9:7; 156:5; 158:21; 163:18;  
 172:12  
 evaluating [1] 158:7  
 Evaluation [1] 8:11  
 evaluation [2] 178:19; 406:16  
 evaluations [1] 44:1  
 evenly [2] 32:4, 6  
 event [6] 17:18; 189:8; 192:11; 219:7;  
 251:13; 380:6  
 events [15] 65:20; 153:17; 156:16; 168:7;  
 169:9, 14, 19; 174:12; 186:11; 348:8;  
 353:14; 367:4, 6; 371:15; 372:16  
 everybody [21] 18:11; 28:8, 15; 29:14;  
 215:2; 233:5; 285:21; 301:10; 308:5, 6;  
 309:7; 328:21; 329:10; 337:15; 359:9, 15;  
 395:11; 397:22; 407:10; 408:5  
 Evidence [1] 144:11  
 evidence [36] 4:17; 38:13; 39:18; 40:8;  
 70:17; 130:7, 13, 18; 132:6; 134:8, 19;  
 135:8; 150:9; 170:8; 190:15; 196:16;  
 239:16; 240:17; 250:7; 302:5; 304:18;  
 306:1; 310:19; 316:7; 319:11; 320:2;  
 322:12; 330:19; 331:18; 332:19; 333:14;  
 341:19;  
 344:8; 381:12  
 evident [2] 182:8; 192:16  
 evolve [1] 283:11  
 Exactly [2] 70:9; 257:20  
 exactly [22] 55:2; 111:9; 116:3; 119:13;  
 124:16; 199:2; 206:21; 257:3; 284:18;  
 294:2, 19; 309:10; 327:20; 335:1; 371:6;  
 390:17; 395:3; 404:10, 16; 405:3; 416:6  
 examination [1] 422:2  
 examine [5] 33:15; 141:21; 171:8; 177:5;  
 423:7  
 examined [7] 38:8; 86:13; 139:8; 143:6;  
 145:4; 147:1; 385:2  
 examines [3] 50:17; 138:15; 194:10  
 examining [1] 181:9  
 example [33] 52:17; 65:4; 88:10; 89:10;  
 112:5; 118:8, 20; 132:21; 133:7; 136:21;  
 142:13; 148:14; 200:1; 201:7; 204:15;  
 212:1; 229:16; 247:5; 250:15; 272:6;  
 317:22; 329:4; 337:14; 338:12, 18; 340:4;  
 342:8; 354:1; 371:10; 384:21; 388:8;  
 391:20;  
 396:2  
 examples [5] 6:19; 114:8; 299:17; 311:14;  
 336:19  
 exceed [1] 57:19  
 exceeds [1] 35:18  
 except [3] 172:3; 249:1; 377:15  
 exception [4] 19:16; 139:19; 189:17;  
 196:19  
 exceptions [1] 8:13  
 excess [6] 183:22; 185:4; 187:18, 21;  
 190:10; 191:7  
 excessive [7] 132:3; 143:20, 22; 157:12;  
 160:14; 161:9; 266:7  
 excessively [2] 5:22; 132:19  
 excited [1] 375:19  
 exclude [7] 10:8; 124:9; 132:22; 187:21;  
 188:2; 266:18; 281:7  
 excluded [6] 74:8; 85:10, 12; 99:18;  
 132:5; 133:13  
 excluding [1] 182:18  
 exclusion [1] 10:9

exclusively [1] 340:6  
 excretion [2] 35:21; 132:14  
 Excuse [2] 250:22; 269:10  
 excuse [1] 32:6  
 exercise [2] 7:6; 394:2  
 exert [1] 28:4  
 exertional [1] 27:20  
 exhibited [1] 5:20  
 exist [3] 196:20; 235:22; 306:7  
 existed [1] 294:6  
 existence [1] 193:14  
 existing [1] 289:12  
 exotic [1] 300:21  
 expand [1] 309:15  
 expect [15] 22:18; 23:1; 52:13; 66:7;  
 68:17; 73:7; 77:11; 94:11; 106:16; 114:15;  
 224:10; 241:12; 255:8; 256:5; 364:20  
 expectation [1] 413:12  
 expected [4] 22:9; 47:18; 113:16; 145:10  
 expensive [1] 320:16  
 experience [20] 7:12; 27:15; 148:15;  
 150:1; 154:16; 163:5; 164:13; 180:5;  
 221:1; 228:2; 229:21, 22; 234:12; 331:18;  
 338:18; 346:21; 349:13; 366:19; 367:16;  
 378:19  
 experienced [1] 158:7  
 experiences [1] 86:1  
 experiment [1] 266:4  
 expert [3] 120:21, 22; 283:6  
 experts [2] 311:5, 8  
 explain [4] 86:5; 236:20; 248:11; 344:5  
 explained [4] 44:14; 146:4; 293:5; 294:5  
 explaining [1] 111:15  
 explanation [3] 254:7; 257:21; 312:10  
 explicitly [1] 345:9  
 exploratory [3] 146:5; 161:18; 255:7  
 explore [1] 227:19  
 explored [3] 43:19; 134:13; 230:3  
 exposing [1] 334:18  
 exposure [6] 35:1; 41:10; 137:2; 169:15;  
 211:4; 247:11  
 expressed [1] 186:15  
 extend [1] 384:22  
 extensive [6] 12:4; 33:5; 43:22; 108:18;  
 176:15; 190:1  
 extent [11] 71:19; 76:2; 95:22; 179:4;  
 186:4; 196:2; 301:3; 316:8; 322:11; 371:7;  
 393:5  
 extra [2] 213:8; 219:14  
 extraordinarily [1] 171:12  
 extrapolate [2] 96:11, 12  
 extrapolating [1] 75:2  
 extreme [2] 125:3; 365:21  
 extremely [3] 126:19; 158:3; 321:15  
 eye [1] 69:21  
 eyeball [1] 71:14  
 eyeballing [1] 72:17

---

- F -

---

faced [3] 53:19; 75:19; 186:19  
 faces [1] 14:13  
 facilitating [1] 407:1  
 factor [3] 19:3; 267:5, 14  
 factors [14] 133:6; 185:22; 227:2; 348:7;  
 12, 20; 349:22; 351:12, 14; 352:15, 16;  
 359:8; 422:3  
 failed [4] 206:18; 235:12, 17; 241:20  
 failure [43] 16:12; 20:22; 25:2; 48:3;  
 65:21; 132:7; 159:4, 5; 169:22; 181:10,  
 11, 17, 21; 182:3, 10, 15, 17, 21; 183:7;

185:11; 192:19; 193:6, 13; 195:1; 206:3;  
 274:10; 290:4; 301:14; 305:16; 315:10;  
 353:12; 357:12, 18; 373:15, 16; 419:20,  
 22; 421:5, 8, 12, 13, 22; 422:11  
 failures [5] 138:6; 140:12; 249:11, 17, 19  
 fair [7] 117:10; 175:19; 198:5; 225:11;  
 312:21; 398:18; 411:17  
 Fairly [1] 160:4  
 fairly [13] 24:8; 54:9; 102:3; 104:15;  
 105:16; 178:6; 285:1; 296:19; 321:18;  
 384:17, 19; 390:14; 409:21  
 fairness [1] 10:12  
 fall [7] 89:5; 364:12; 405:14, 15, 16;  
 410:11  
 familiar [1] 190:3  
 fare [2] 335:8, 346:15  
 fashion [4] 46:5; 153:9; 256:18; 320:7  
 fast [3] 290:12; 302:19, 20  
 faster [1] 320:16  
 fatigue [4] 18:2; 147:21; 149:12; 310:9  
 fault [2] 407:8, 10  
 favor [1] 149:4  
 favorable [4] 22:20; 149:6; 190:19; 192:13  
 favored [1] 248:7  
 FDA [24] 4:14; 5:1; 6:16; 9:5, 17; 10:7;  
 113:11; 149:16, 18; 162:8; 257:17;  
 376:15; 384:17; 405:6, 20; 406:5, 19, 21;  
 408:16, 22; 409:6; 413:6; 417:17; 423:6  
 fear [2] 367:11; 408:12  
 features [3] 6:9; 45:1; 196:14  
 feed [1] 78:6  
 feel [15] 28:2; 29:1; 169:1; 333:1; 335:5;  
 7; 338:19; 339:7; 344:19, 20; 356:8;  
 406:8; 407:17; 408:21  
 feeling [6] 31:9; 105:18; 116:18; 372:4;  
 376:10; 405:5  
 feels [3] 24:3; 333:17; 344:13  
 feet [2] 406:5, 20  
 felt [6] 6:2; 252:6; 260:13; 319:10; 335:8;  
 384:17  
 female [8] 44:11; 167:13, 14, 22; 171:13;  
 277:18; 278:8; 357:6  
 females [9] 32:7; 93:1; 95:20, 22; 98:16;  
 143:5; 167:12; 171:14; 220:4  
 fewer [2] 170:4; 423:5  
 FG [1] 336:1  
 fib [14] 12:16; 13:11; 22:16; 85:11; 253:5;  
 254:5; 267:21; 279:1; 322:1; 323:13;  
 324:3; 422:18; 423:4  
 fibrillating [1] 308:5  
 fibrillators [1] 223:10  
 fibrillity [1] 340:3  
 fiddle [1] 240:12  
 fide [1] 300:1  
 field [1] 228:11  
 fifteen [1] 368:16  
 fifty [1] 284:13  
 figure [20] 46:10; 61:6; 63:9; 97:20; 134:1;  
 154:18; 164:12; 172:1; 194:15; 220:12,  
 13; 232:8; 233:12; 245:12, 15; 291:16;  
 300:11; 351:16; 355:5; 359:15  
 final [5] 125:7; 248:15; 277:14; 280:3;  
 299:9  
 financial [3] 8:8; 10:7, 13  
 find [12] 53:21; 79:4; 115:19, 20; 170:13;  
 289:7; 301:19; 314:19; 315:2; 389:5;  
 394:8; 403:11  
 finding [6] 134:11; 149:22; 284:3; 344:9,  
 11; 396:13  
 findings [7] 37:1; 135:1; 138:17; 140:3;  
 144:16; 267:8; 352:12

Fine [1] 236:10  
 fine [4] 61:16; 227:14; 369:15; 400:21  
 finish [2] 199:22; 219:14  
 finite [1] 371:17  
 fire [1] 399:6  
 firm [2] 10:14; 411:7  
 firms [2] 8:10; 10:6  
 First [4] 96:21; 175:20; 223:16; 325:14  
 Firstly [1] 47:16  
 firstly [1] 33:19  
 FISHER [1] 239:4  
 Fisher [1] 239:3  
 fit [1] 410:9  
 fits [2] 80:11; 180:5  
 Five [1] 294:6  
 five [11] 123:6, 7; 136:14; 164:5; 176:17;  
 284:12; 297:8; 306:18; 333:9; 354:6;  
 367:14  
 five-fold [1] 367:20  
 fixed [6] 30:4; 262:9, 11; 263:7; 303:8;  
 351:2  
 fixes [1] 365:21  
 flash [1] 62:20  
 Flecainide [7] 20:6; 128:14, 19; 180:1;  
 416:15; 417:1, 2  
 flip [2] 286:2; 411:12  
 floor [1] 68:6  
 flow [4] 35:2; 89:15; 90:2; 95:9  
 fluconazole [1] 39:19  
 fluctuation [1] 238:12  
 fluke [1] 256:5  
 fluoxetine [1] 420:15  
 Fluramine [1] 6:20  
 flutter [36] 5:12; 22:4, 9, 16, 17; 23:2, 3, 5,  
 6; 130:20; 131:7; 134:4, 10, 22; 135:10,  
 12; 136:1; 137:8, 10; 138:17; 142:9, 18;  
 143:4; 144:13; 145:3, 19; 150:5, 10;  
 152:7, 20; 322:2, 4, 7; 323:13, 18; 324:4  
 flying [1] 374:15  
 focal [1] 224:8  
 focus [6] 72:22; 78:2; 153:15, 21; 169:9;  
 318:7  
 focused [2] 86:10; 283:16  
 focuses [2] 159:4, 5  
 focusing [4] 113:6; 155:3; 172:9; 257:21  
 fold [1] 367:14  
 folks [5] 82:1; 97:11; 233:17; 282:16;  
 387:17  
 follow [10] 57:22; 59:20; 176:20; 187:7,  
 17; 200:12; 216:18; 270:18; 278:16;  
 283:12  
 follow-up [9] 156:6; 164:16; 175:6, 13;  
 179:14; 287:5; 307:11; 315:7; 402:4  
 followed [2] 220:11; 223:5  
 Following [1] 45:20  
 following [12] 8:3, 13; 20:13; 28:14; 64:13,  
 20, 22; 143:3; 181:4; 206:14, 16; 239:8  
 follows [1] 293:17  
 font [1] 288:20  
 Food [1] 339:3  
 food [1] 34:11  
 foregoing [1] 196:22  
 foregone [1] 221:20  
 foresee [1] 397:12  
 foreseeable [2] 19:9; 321:15  
 forge [1] 404:6  
 forget [1] 233:3  
 forging [1] 404:5  
 forgot [1] 98:9  
 form [9] 9:14; 16:16; 19:14; 30:1; 103:13;  
 252:4; 396:13; 409:18, 19

formal [1] 409:8  
 formally [1] 319:6  
 format [1] 161:1  
 former [1] 10:2  
 forms [3] 18:7; 226:19; 350:11  
 formula [1] 133:3  
 forth [6] 11:1; 65:21; 250:20; 254:12;  
 273:13; 390:6  
 Fortunately [2] 192:20; 295:12  
 forward [7] 4:7; 11:8; 120:6; 148:7; 283:9;  
 341:4; 384:18  
 found [4] 5:8; 142:1; 333:6; 343:9  
 four [19] 44:20; 100:21; 104:18; 119:4;  
 139:1, 10; 140:8; 141:22; 142:2; 153:21;  
 156:20, 21; 168:7, 10, 12; 241:15; 244:7,  
 16; 253:4  
 FP [1] 369:20  
 fraction [10] 48:16; 55:16, 21; 124:6, 12;  
 158:13; 369:19; 387:17; 389:6; 396:11  
 fractions [3] 48:9; 55:6; 336:20  
 frame [6] 42:10; 62:22; 70:6; 323:5;  
 324:4; 371:5  
 framework [3] 235:6, 10, 16  
 frameworks [1] 235:1  
 Framingham [2] 342:8; 346:21  
 frankly [1] 77:15  
 free [3] 25:5; 234:4; 339:3  
 Freedom [2] 4:13; 8:18  
 freedom [1] 241:14  
 frequency [13] 145:17; 148:2, 8, 11, 13,  
 16; 149:4, 10; 152:16; 278:17; 279:2;  
 286:7; 290:2  
 frequent [4] 18:6; 148:15; 193:6; 368:17  
 frequently [4] 17:13; 129:18; 162:19;  
 368:19  
 FRIEDRICH [41] 130:15; 199:6, 10;  
 200:16; 201:13, 22; 202:2, 17; 203:9;  
 204:4, 9, 12, 19; 205:7, 18, 20; 206:4, 19;  
 207:4; 208:6; 258:10; 260:3, 13; 261:2;  
 263:1; 266:13; 268:15, 22; 269:3, 7, 10,  
 13; 270:22; 271:7, 13, 17, 22; 272:12, 16,  
 20; 275:20  
 Friedrich [7] 13:18; 199:5; 200:14; 248:17;  
 258:8; 266:11; 268:13  
 front [3] 10:21; 11:7; 417:10  
 full [2] 8:14; 413:11  
 fun [1] 198:12  
 functional [7] 70:10; 139:21; 159:14;  
 309:20; 385:1  
 functionally [1] 75:7  
 functioning [2] 25:22; 310:4  
 fundamental [1] 281:21  
 funny [1] 327:22  
 futile [1] 78:4  
 future [2] 19:9; 398:20

## - G -

gain [2] 389:2; 421:17  
 gamut [1] 127:19  
 Ganley [1] 149:16  
 gather [1] 283:2  
 gathered [2] 126:3; 316:1  
 Gatorade [1] 125:9  
 Gault [1] 244:4  
 gave [5] 83:2; 230:12; 239:7; 250:11;  
 391:13  
 Gayle [2] 232:22; 233:6  
 gee [1] 68:17  
 geez [1] 302:17  
 gender [22] 44:9, 13, 14, 16; 77:20; 78:20;

79:4; 95:18; 133:6; 145:4; 156:11; 157:14,  
 22; 162:1; 167:22; 168:3; 171:11; 185:18;  
 277:18; 351:12; 357:6; 358:9  
 generates [1] 15:18  
 generation [2] 114:3; 116:2  
 generic [2] 12:2; 312:2  
 genetic [1] 312:3  
 gentlemen [6] 11:15; 14:2; 32:19; 130:17;  
 153:5; 178:17  
 germane [2] 75:22; 285:19  
 gets [10] 63:22; 75:18; 103:2; 117:13;  
 234:14; 235:13; 310:5; 354:5; 368:6;  
 384:13  
 GFR [1] 35:18  
 GI [2] 35:2; 90:2  
 give [39] 4:6; 51:12; 67:8; 76:5, 21; 78:12;  
 79:15; 84:3; 85:21; 99:5; 101:8; 113:17;  
 122:22; 146:6; 204:12; 213:19; 227:10,  
 18; 237:4; 276:17; 291:14; 299:13; 315:8;  
 317:3; 325:10, 11, 12; 329:10; 338:7;  
 351:19; 352:20; 355:11; 358:5, 12;  
 368:17; 398:18; 413:16, 22; 422:5  
 given [29] 5:20; 13:15; 48:4; 64:7; 82:16;  
 86:1; 101:4; 110:16; 115:11; 150:5; 161:6;  
 188:14; 210:7; 220:8; 222:18; 231:17;  
 240:13; 259:19, 20, 21; 285:1; 288:5, 20;  
 331:10; 351:11; 377:19; 391:1; 401:12;  
 403:2  
 gives [5] 71:18; 114:15; 116:18; 342:4;  
 361:12  
 giving [8] 60:17; 220:8; 252:19; 347:5;  
 349:11; 374:9; 378:15; 395:20  
 glad [1] 24:21  
 glaring [1] 185:4  
 Glen [3] 207:11; 239:3; 261:5  
 global [1] 113:8  
 goal [2] 195:14; 332:5  
 God [1] 408:12  
 goes [9] 31:6; 50:11; 54:17; 71:2; 72:5;  
 100:13; 267:8; 283:1; 405:9  
 Goodbye [1] 385:12  
 goodness [2] 92:12; 285:4  
 gospel [1] 412:6  
 gotten [5] 104:10; 115:12; 296:3; 327:3;  
 393:2  
 grab [1] 115:10  
 GRABOYS [23] 96:16; 234:6, 11, 17;  
 272:3; 273:4, 22; 274:4, 22; 275:16;  
 314:14; 320:19; 325:13; 337:3; 350:5;  
 357:11; 370:5; 377:10; 383:2; 387:15;  
 402:14; 408:7; 415:18  
 Graboys [4] 96:15; 185:7; 275:14; 307:18  
 graded [1] 322:14  
 grant [2] 231:1; 317:12  
 granted [2] 8:15; 355:7  
 graph [9] 49:19; 55:5, 19; 62:6, 8, 15;  
 72:18; 148:10; 229:3  
 graphical [2] 79:21, 22  
 Great [1] 251:19  
 great [9] 15:17; 175:6; 242:11; 274:15;  
 275:11; 276:11; 279:2; 378:15; 420:3  
 greater [14] 34:4; 50:1, 10, 11; 95:22;  
 116:4; 123:1; 218:11, 17, 18; 295:9, 15;  
 353:12; 390:12  
 greatest [3] 57:12, 14; 147:12  
 green [1] 203:17  
 Grines [8] 21:20; 23:9; 51:13; 55:3; 207:1;  
 212:16; 215:19; 318:16  
 gross [1] 52:7  
 grossly [1] 77:16  
 ground [4] 299:17; 397:1; 404:5, 6

grounds [3] 388:8, 22; 389:8  
 Group [1] 4:10  
 group [44] 25:11; 40:9; 42:22; 58:20;  
 59:4; 96:8, 9; 102:7; 135:15; 143:9, 11,  
 21; 144:4; 145:19; 147:1; 148:22; 149:5,  
 8; 154:7; 156:17; 172:22; 177:16; 188:12;  
 189:2, 8; 200:20; 201:19, 20; 202:8;  
 204:20; 208:2; 211:1; 217:15; 228:6;  
 263:11,  
 16; 264:1; 266:19; 290:9; 293:9; 296:6,  
 12; 310:14; 423:5  
 grouping [1] 42:22  
 groups [26] 36:17; 104:22; 136:15; 139:2,  
 11; 140:9, 18, 22; 156:15; 160:14; 163:22;  
 164:4; 169:7; 178:7; 192:13; 195:11;  
 202:9; 203:15; 205:10; 227:3; 241:15;  
 270:14; 280:12; 385:1  
 guaranteed [1] 300:1  
 guest [1] 9:17  
 guests [1] 10:18  
 guidance [2] 82:17; 299:14  
 guide [2] 116:6, 7  
 guidelines [6] 226:10, 12; 239:11; 412:1,  
 3; 413:7  
 gun [1] 363:10  
 gut [2] 34:8; 89:15  
 guy [1] 129:7  
 guys [7] 301:17; 367:17; 396:22; 397:16;  
 399:5, 17; 410:14

## - H -

hadn't [2] 59:13; 124:11  
 hairy [1] 256:2  
 half [23] 32:3; 47:10; 50:13; 56:2; 58:21;  
 96:7; 100:10, 20, 21; 101:1; 102:12, 14,  
 17; 133:10, 17; 139:16; 176:2, 16; 210:14;  
 265:1; 285:21; 306:13; 371:13  
 half-life [2] 45:13; 264:22  
 half-lives [1] 58:16  
 hand [3] 17:21; 333:1; 406:3  
 handily [1] 239:18  
 handle [1] 92:15  
 handled [3] 270:19; 271:11; 374:4  
 hang [1] 314:15  
 happening [2] 245:4; 288:12  
 happens [13] 97:10, 16; 112:21; 122:18;  
 189:15; 208:13; 257:22; 264:11; 318:2;  
 364:13; 367:10; 386:13; 400:7  
 happy [2] 236:20; 289:1  
 hard [7] 10:19; 55:16; 75:16; 103:18;  
 232:11; 393:5; 406:15  
 harder [1] 403:20  
 harm [7] 191:6; 318:2, 4, 11; 324:12;  
 334:7; 345:21  
 harmed [2] 336:21; 346:4  
 hasn't [3] 126:15; 381:2; 420:15  
 hat [2] 324:17  
 hate [1] 72:16  
 hates [1] 308:6  
 haven't [19] 56:20; 61:5, 14; 77:8; 109:6;  
 209:4; 242:4; 270:2; 275:1; 278:21;  
 297:21; 302:3; 319:3; 332:19; 382:18;  
 383:13; 388:7; 394:14; 402:9  
 havoc [2] 367:22; 369:12  
 hazard [15] 142:17; 143:19; 160:2;  
 161:21; 173:11; 181:18; 182:12; 186:12,  
 13; 189:20; 190:20; 249:22; 250:1, 11;  
 260:18  
 hazards [2] 348:6; 349:21  
 head [12] 85:13; 374:19, 22; 380:12;

417:14, 22; 419:19, 20  
 heading [1] 299:16  
 heads [1] 57:5  
 health [2] 21:9, 12  
 healthy [5] 5:19; 44:11; 109:2; 165:19; 229:10  
 hear [26] 17:8; 31:5, 18; 61:9; 91:21; 178:14; 216:21; 227:10; 233:8; 238:16; 250:18; 257:13; 269:20, 21; 274:16; 277:15, 21; 291:1; 297:10; 310:7; 325:16; 355:22; 363:15; 391:9; 397:5; 407:14  
 heard [30] 18:22; 67:10; 68:5; 154:4, 13; 179:8; 180:1, 9, 14; 181:7; 183:20; 184:3, 11; 193:7, 21; 196:9; 222:12; 296:22; 324:2; 329:10; 341:2, 3; 343:22; 345:12; 346:12; 347:9; 391:10; 394:14; 403:2; 404:18  
 Hearing [1] 7:19  
 hearing [2] 282:12, 13  
 hearings [1] 356:9  
 heck [1] 233:21  
 held [1] 373:3  
 hell [1] 374:18  
 help [12] 51:16; 52:2; 85:21; 96:18; 223:3; 238:22; 275:8; 290:8; 305:13; 314:15, 22; 350:19  
 helped [1] 410:15  
 helpful [9] 104:2; 108:14; 113:9; 219:17; 275:6; 315:1, 3, 4; 345:1  
 helps [3] 76:20; 229:11; 288:11  
 hemodynamic [5] 47:17; 55:5, 8, 10; 391:19  
 hemodynamics [1] 48:19  
 hepatic [2] 44:6; 52:10  
 hetero [1] 312:4  
 hey [1] 87:20  
 hiding [3] 112:10, 12; 371:8  
 high [26] 25:22; 34:7; 35:17, 22; 36:18; 52:21; 64:9; 92:11; 93:7, 10; 134:20; 138:13; 144:15; 151:21; 154:6; 159:20; 179:2; 215:5; 227:22; 277:5; 280:20; 286:8; 362:10; 372:19; 398:2  
 higher [42] 44:10, 20; 62:15; 64:8; 79:7; 95:6; 111:3; 183:3, 4; 188:14; 228:7; 230:16; 257:10; 258:2; 276:16; 279:20; 280:7, 10, 14; 281:10; 290:21; 293:8; 311:11; 312:22; 313:20; 320:15; 321:16, 17; 322:4, 7; 323:9, 21; 330:21; 331:2; 347:5; 369:5; 372:17, 21; 373:13; 375:13; 400:17  
 highest [6] 28:11; 244:9, 10; 354:1; 362:15  
 highly [9] 17:14; 21:15; 91:8; 138:2; 224:12; 308:21; 379:7, 17; 382:19  
 hint [1] 270:8  
 historically [2] 251:15; 338:13  
 history [4] 132:8; 230:5; 240:20; 251:12  
 hit [2] 209:5; 363:10  
 hoc [1] 127:17  
 hold [1] 312:21  
 holder [1] 228:20  
 holding [1] 399:5  
 hole [2] 216:21; 382:22  
 holes [1] 127:6  
 home [1] 59:12  
 homogenous [1] 312:5  
 honestly [2] 349:19; 397:1  
 nonesty [1] 241:21  
 hook [1] 314:15  
 hope [5] 30:4; 51:5; 224:17; 274:10; 380:3

hopefully [3] 27:1; 77:18; 390:11  
 hoping [1] 315:13  
 horizontal [1] 49:18  
 hormone [3] 43:15; 93:15; 94:10  
 horrendous [2] 96:20; 398:14  
 hospital [31] 15:18, 19; 16:1, 5; 23:11; 45:22; 58:6; 60:6; 62:3; 76:7; 77:19; 97:17, 18; 132:12; 184:13; 196:11; 233:15, 16, 18, 22; 297:8; 298:5; 299:22; 311:12; 316:7; 361:17; 366:5; 367:7; 370:17; 372:13; 403:16  
 hospitalization [21] 100:8; 166:21; 170:10, 11; 181:9, 14, 17; 182:3, 10, 16, 17, 21; 183:6, 9, 12, 14; 356:18; 367:2, 5; 368:5; 402:6  
 hospitalizations [4] 169:21; 170:4, 6; 422:13  
 hospitalized [3] 76:4; 97:13; 136:3  
 hospitals [6] 176:2, 4; 402:10; 405:9; 406:11; 410:5  
 host [1] 408:8  
 hour [5] 31:6; 34:14; 136:8; 265:1; 314:4  
 hours [15] 30:21; 31:1, 6; 45:13; 57:16; 58:22; 102:19; 133:14; 150:17; 151:4, 15; 218:16; 264:19; 265:5; 403:18  
 HRT [3] 94:20; 95:4, 7  
 huge [4] 55:15; 318:20; 325:14; 336:15  
 hundred [3] 177:14; 242:21; 317:11  
 hundreds [3] 105:6; 108:2; 292:1  
 Hung [1] 149:16  
 hypertensive [1] 363:16  
 hypertensives [1] 347:1  
 hypokalemia [1] 124:17  
 hypokalemic [1] 334:16  
 hypothesis [5] 114:1, 3; 116:2; 242:14; 310:22  
 hypothetical [2] 200:6; 225:16

— | —

I'd [1] 237:4  
 I've [15] 50:5; 59:6; 67:10; 102:19; 119:18; 126:7; 152:5; 242:8; 288:3, 4; 338:2; 343:22; 385:12; 393:1  
 IA [1] 190:4  
 Ibutilide [3] 19:22; 20:1; 382:4  
 IC [1] 190:11  
 idea [13] 79:15; 216:1; 227:18; 231:15; 242:20; 245:11, 12; 275:2; 362:21; 367:17; 396:19; 404:8; 409:4  
 identical [10] 140:20; 164:4; 171:8; 172:13; 174:21; 190:21; 193:15; 194:13; 287:21; 394:13  
 identifiable [2] 106:17; 122:8  
 identified [8] 43:10; 134:15; 144:1; 166:13, 18; 351:12; 353:4; 421:1  
 identifies [1] 116:4  
 identify [5] 4:8; 36:2; 105:15, 17; 197:7  
 identifying [1] 174:6  
 ideology [1] 352:9  
 idiosyncratic [1] 240:1  
 ignorant [4] 129:7, 11; 313:22; 314:1  
 ignore [1] 252:12  
 ignored [1] 403:8  
 ignoring [1] 254:8  
 ill [4] 277:16, 19; 278:5; 324:5  
 IKR [3] 49:3; 278:7; 312:14  
 Ileana [11] 321:10; 341:11; 351:5; 372:11; 378:16; 389:17; 402:17; 416:2, 8; 419:13; 421:5  
 illustrates [1] 21:4

IM [1] 369:20  
 imagination [1] 301:2  
 imagine [3] 114:16; 233:14; 299:21  
 imbalances [2] 157:6, 8  
 immediate [2] 34:20; 89:21  
 immediately [2] 28:12; 167:15  
 immobilized [1] 308:6  
 impact [10] 42:11; 182:15, 20; 191:13; 209:1; 297:2; 299:5; 359:20; 401:13; 409:4  
 impaired [7] 73:11; 95:22; 191:2; 266:22; 267:5; 294:14; 419:17  
 impairment [6] 36:13; 44:6; 47:22; 159:15; 309:20; 418:11  
 impart [1] 59:16  
 impeachment [1] 356:9  
 imperfect [1] 288:2  
 imperfection [1] 192:21  
 impetus [1] 399:9  
 implement [2] 297:1; 397:3  
 implementation [1] 215:4  
 implemented [5] 45:21; 133:21; 237:15; 296:20; 396:15  
 implication [2] 124:20; 407:8  
 implications [1] 198:15  
 implies [3] 34:8; 235:4; 360:14  
 importance [4] 68:3; 166:3; 193:9; 354:11  
 importantly [2] 93:12; 172:22  
 imposed [2] 300:19; 398:14  
 imprecise [3] 115:6, 18; 117:5  
 impressed [2] 351:10; 379:10  
 impression [4] 84:7, 14; 103:14; 121:8  
 impressive [2] 127:4; 224:7  
 impressively [1] 126:3  
 improper [1] 402:20  
 improperly [1] 106:21  
 improve [4] 182:3; 315:12, 16; 336:20  
 improved [2] 146:20; 330:22  
 improvement [12] 145:22; 146:17, 18; 147:3, 9; 149:21; 150:1; 330:7, 9; 331:7; 336:10, 15  
 improvements [1] 131:3  
 in-hospital [5] 161:2; 360:20; 368:13; 402:7; 403:19  
 in-patient [6] 160:19; 164:22; 166:13, 19; 169:2; 306:20  
 inadvertently [1] 406:6  
 inappropriate [4] 77:10; 231:17; 367:12, 13  
 incapacitated [2] 17:1; 28:2  
 inception [1] 210:21  
 incidence [14] 12:22; 62:17; 123:1, 3; 165:11; 262:6; 302:1; 311:11; 351:21; 352:4; 369:7, 8; 370:17; 371:3  
 incidences [1] 366:6  
 incident [1] 123:5  
 incidents [1] 371:2  
 include [16] 18:11, 18; 20:6; 83:11; 154:6; 161:12; 165:17; 185:18; 195:3; 206:2, 4, 17; 212:11; 216:13; 272:4; 375:20  
 included [21] 38:10; 131:12, 17; 138:6; 140:10; 145:7; 146:13; 165:20; 172:16; 212:11; 213:3, 4; 215:13, 14; 217:3, 12; 223:4; 248:18; 251:14; 253:7; 263:12  
 includes [3] 46:14; 175:7; 216:3  
 incompletely [1] 75:3  
 inconsistent [2] 242:7; 385:2  
 incorporated [3] 41:16; 50:2; 210:7  
 incorrect [1] 177:12  
 increase [30] 13:4; 15:13; 34:21; 35:1; 37:21; 41:10; 48:15; 55:15; 66:11; 84:13;

- 95:8; 97:17; 104:8; 121:12, 22; 122:3; 124:10, 12, 22; 125:2; 133:16; 148:13; 169:6; 171:9; 188:13; 200:9; 235:8; 282:1; 311:16  
 increased [18] 5:8; 16:13; 35:2; 89:15; 122:5; 133:19; 152:17; 170:9; 171:13, 18; 189:10; 265:10; 275:7; 294:10; 349:22; 352:4; 353:20; 369:6  
 increases [3] 122:2; 351:21; 353:5  
 increasing [7] 15:15; 89:13; 121:12; 140:15, 16; 264:20; 266:10  
 increasingly [1] 224:7  
 incredible [1] 374:5  
 Incredibly [1] 359:3  
 independent [4] 44:6; 267:5; 330:6; 339:10  
 index [8] 48:15, 21; 68:4, 11; 72:22; 158:14; 265:9; 266:10  
 Indiana [2] 32:20; 76:6  
 indicate [4] 36:19; 40:22; 96:3; 276:12  
 indicated [2] 43:7; 45:22  
 indicates [5] 34:18; 35:9, 11; 36:1; 44:4  
 indicating [1] 51:3  
 indication [7] 17:12; 20:1; 129:19; 177:9; 292:13; 307:8; 370:11  
 indications [4] 21:3, 7; 308:21  
 indigestion [1] 198:5  
 indirect [1] 87:5  
 individual [14] 36:12; 53:9; 59:22; 92:21; 110:19; 114:11; 163:13; 164:14; 218:15; 279:16, 17; 287:17; 390:5; 418:14  
 individualization [5] 12:21; 47:14; 56:1; 161:14; 174:6  
 individualize [2] 75:13, 16  
 individualized [3] 45:20; 154:21; 165:1  
 individualizing [3] 33:18; 76:1; 265:20  
 individually [1] 248:3  
 individuals [13] 95:6; 248:2, 4, 10; 249:7, 8, 9, 10; 250:19; 251:7; 272:4; 312:9  
 inevitable [1] 153:12  
 infancy [1] 19:8  
 infarction [5] 132:6; 159:6; 190:13; 192:2, 9  
 infarcts [1] 191:1  
 inference [1] 250:12  
 infinite [1] 306:13  
 infinitely [1] 27:22  
 influence [8] 43:20; 52:18; 246:1; 355:3, 6; 408:22; 409:3, 10  
 influenced [1] 310:16  
 influences [1] 410:3  
 influencing [2] 408:20  
 Information [2] 4:13; 8:18  
 information [43] 27:1; 51:12; 61:22; 87:3, 4; 88:3; 104:1; 115:22; 155:9; 167:9; 176:21; 177:2; 206:20; 225:2; 227:6; 231:2; 232:6; 256:13, 15, 20; 268:14; 270:4; 276:4; 283:1, 3, 10; 284:10; 285:9, 17; 286:9; 288:19; 304:14, 15; 313:18; 326:20; 329:6; 350:18; 399:10, 13; 413:21; 414:14; 420:20  
 informative [1] 161:20  
 inhibit [6] 37:18; 39:17, 19; 42:12; 53:5; 92:13  
 inhibited [1] 39:14  
 inhibiting [1] 39:17  
 inhibition [9] 38:20; 41:3, 11, 20; 42:2; 43:13; 103:5; 104:6; 114:15  
 inhibitor [6] 39:10; 41:8, 9; 49:3; 52:4; 80:12  
 inhibitors [18] 38:12, 15; 39:13; 40:5, 7; 42:17, 19; 52:12; 54:20; 88:18; 105:1, 2, 3, 7; 108:21; 118:14; 137:14; 140:2  
 inhibits [1] 103:8  
 initial [6] 70:18; 138:7; 140:13; 163:10; 362:22; 397:19  
 initially [2] 150:5; 220:18  
 initiate [1] 25:16  
 initiated [5] 45:22; 132:12; 166:9; 172:5; 213:21  
 initiation [15] 132:18; 136:3; 160:20; 165:1; 166:2, 13; 169:2; 172:11; 174:5; 184:13; 196:12; 278:12; 291:18; 293:4; 306:21  
 inject [1] 407:16  
 injuries [1] 6:18  
 inpatient [2] 278:12; 291:18  
 insert [1] 75:11  
 insidious [1] 18:4  
 insight [2] 145:10; 146:6  
 insignificant [1] 177:1  
 insisted [2] 293:3; 388:10  
 insistence [1] 169:3  
 insisting [1] 331:7  
 inspection [1] 405:9  
 instance [4] 166:5; 171:11; 201:14; 215:8  
 Institute [1] 9:9  
 instituted [1] 396:11  
 institution [4] 9:2; 24:2, 6; 264:13  
 instructed [2] 82:20; 83:4  
 instructing [1] 82:14  
 instructions [3] 60:18; 83:2; 352:19  
 instruments [7] 145:13; 146:1, 3, 19; 147:4, 9, 15  
 intend [2] 172:18; 173:5  
 intended [1] 207:11  
 intends [1] 70:2  
 intense [1] 397:20  
 intent [1] 211:4  
 intention [7] 138:4, 22; 156:4; 158:22; 161:12; 163:18; 368:2  
 interactants [1] 42:3  
 interacting [1] 281:2  
 interactions [24] 34:5, 16; 36:3; 40:4; 42:16; 52:1; 68:2; 80:10; 86:2; 111:15, 16; 113:1; 125:13, 17; 126:12; 128:10; 282:5; 351:13; 358:16; 359:1; 395:18; 419:15; 420:21, 22  
 intercept [2] 74:20; 75:1  
 interest [9] 8:1, 4, 10, 12; 10:7, 12; 41:1; 114:13; 237:6  
 interested [6] 27:15; 90:11; 214:17; 260:19; 288:8; 384:9  
 interesting [8] 30:16; 67:20; 84:5; 191:16; 256:8; 374:16, 20; 401:1  
 interests [2] 8:8; 9:19  
 interfere [1] 310:3  
 intermediate [1] 103:4  
 intermittent [1] 7:3  
 internists [1] 176:5  
 interpret [4] 243:14; 245:19; 336:3; 339:6  
 interpretation [4] 246:4; 330:17; 348:11; 359:22  
 interpreted [1] 352:13  
 interpreting [1] 251:22  
 interrupt [1] 294:21  
 interval [45] 5:22; 49:4; 51:1; 56:2; 57:7; 58:7, 10; 62:9, 14, 16, 18; 63:20; 64:7, 11, 16; 65:4; 68:12; 82:13; 83:3, 9, 14; 121:5, 11, 21, 22; 124:18; 125:18; 230:15; 247:16; 262:18; 263:2; 268:11; 277:17; 302:14; 303:3; 307:4; 311:17; 312:12; 313:2; 316:3; 343:11; 380:5; 400:16; 402:22; 403:1  
 intervals [14] 56:5; 81:20; 124:3; 148:4; 156:18; 158:4; 186:15; 242:5; 261:6; 284:22; 379:15; 403:4; 413:2, 17  
 intervention [3] 167:3, 6; 318:1  
 interventional [3] 86:10; 88:1; 102:6  
 intestinal [1] 34:9  
 intimate [1] 214:10  
 intimately [1] 113:16  
 intolerant [4] 388:9, 11, 14, 15  
 intracranial [1] 316:16  
 intravenous [1] 349:14  
 intravenously [1] 48:4  
 intriguing [1] 170:13  
 intrinsic [3] 40:17; 118:17; 275:7  
 intrinsically [1] 380:17  
 introduce [4] 32:15; 152:22; 235:3; 294:11  
 introduced [4] 47:3; 246:21; 294:7, 11  
 introducing [1] 13:21  
 invasive [1] 47:20  
 inverse [2] 96:12; 264:15  
 invest [1] 107:3  
 investigator [1] 82:14  
 investigators [8] 48:2; 83:4; 127:18; 207:20; 281:3; 298:9; 316:2; 411:8  
 invite [1] 11:8  
 invited [1] 9:17  
 involve [1] 10:5  
 involved [8] 9:2, 15; 17:3; 39:6; 135:11; 170:16; 176:3; 262:16  
 involvement [4] 9:6, 11; 10:9, 13  
 involves [1] 353:1  
 involving [2] 34:6; 379:6  
 ironic [1] 256:1  
 irregular [1] 82:10  
 irrespective [1] 301:22  
 irreversible [2] 324:12; 334:6  
 ischemia [10] 162:9; 226:2, 15; 348:8; 349:7, 11, 16; 350:8, 18; 353:10  
 ischemic [2] 194:21; 250:16  
 iso [4] 40:21, 22; 41:4; 53:5  
 issue [44] 8:4; 36:4; 76:14; 90:2; 94:21; 97:12; 99:4; 101:16; 117:14; 154:14; 160:9; 165:8; 186:4, 18; 207:13; 208:13; 210:2; 214:14; 221:1; 224:16; 230:9; 242:11, 22; 275:1, 2; 281:18; 303:11; 306:17; 310:2; 313:14; 317:6, 12, 14; 318:1, 4; 333:12; 345:13; 348:4; 353:1; 384:5; 395:19; 397:8; 401:4, 17  
 issues [27] 11:4; 24:18; 30:16; 31:17; 84:5; 153:9; 156:12; 165:5; 168:5; 169:20, 21; 171:6; 176:12; 198:12, 14; 207:19; 225:16; 237:6; 275:4; 281:17; 339:21; 354:15; 358:2; 385:11; 404:2; 408:9; 421:1  
 item [1] 177:4  
 items [1] 108:4  
 itroelectric [1] 82:22  
 IV [3] 5:15; 101:21; 131:13  
 iviamerine [1] 349:16

jack [2] 302:19, 21  
 January [2] 4:12; 8:1  
 JCAH [1] 406:14  
 Jeremy [15] 13:13, 21; 22:1; 29:17; 32:17; 223:8; 225:13; 234:8; 287:16; 309:14;

310:12; 312:17; 324:22; 331:12; 337:14  
 Joan [11] 7:20; 31:21; 117:6; 278:16;  
 321:20; 342:14; 359:11; 373:7; 390:8;  
 403:13; 420:8  
 job [5] 126:17; 198:16; 313:6; 348:15;  
 117:18  
 John [1] 29:22  
 joined [1] 345:13  
 Joint [1] 406:14  
 Journal [1] 239:13  
 judgement [11] 26:20; 59:16; 97:3; 309:4;  
 338:17; 339:2, 4; 389:15; 390:18; 391:16;  
 394:19  
 judgements [1] 26:18  
 judging [1] 409:2  
 judgment [1] 392:11  
 jump [1] 110:4  
 jumping [1] 355:21  
 junior [1] 176:10  
 justification [2] 142:11; 256:21  
 justified [1] 260:13

## - K -

Kaplan-Meier [24] 69:9; 137:20; 138:7, 21;  
 139:6; 140:13; 156:5, 13; 158:21; 159:17;  
 163:19; 164:3; 181:13; 191:21; 193:1;  
 203:10; 206:20; 207:4, 13; 208:20;  
 248:13; 264:15; 288:4; 375:10  
 keep [11] 14:6; 28:9; 30:15; 59:8; 62:2;  
 273:2; 327:8; 331:21; 337:19; 342:11;  
 369:1  
 keeping [1] 267:11  
 keeps [1] 70:14  
 Ketoconazole [24] 39:14, 16, 20; 40:1;  
 41:7, 15, 22; 42:4; 43:12; 52:5; 53:2;  
 37:11, 14, 20; 95:20; 96:1, 3, 5; 104:13,  
 15; 106:5; 116:6; 118:8; 127:4  
 key [7] 119:10; 280:11; 316:11; 352:16;  
 354:6; 397:10  
 kick [1] 386:21  
 kidney [3] 35:7; 37:8; 40:14  
 kilograms [1] 98:10  
 kinds [4] 61:14; 66:17; 189:18; 324:22  
 kinetic [6] 75:5; 106:2, 12; 111:7, 10;  
 422:3  
 kinetics [2] 75:7; 113:1  
 knowing [1] 380:17  
 knowledge [5] 15:14; 255:18; 380:18, 22;  
 412:16  
 Konstam [4] 8:15; 85:15; 280:21; 422:16  
 Kowey [7] 8:16; 21:21; 51:13; 61:21;  
 167:19; 253:4, 12  
 Kox [1] 249:22

## - L -

L-Dopamine [1] 99:12  
 label [10] 53:6; 54:11; 91:13; 232:18;  
 351:17; 372:9; 414:5, 9; 419:5; 420:5  
 labeled [3] 20:1; 85:17; 358:2  
 labeling [23] 18:20; 54:12; 224:16; 230:9;  
 269:18; 270:2, 5, 11; 282:10, 19; 283:1,  
 11, 22; 383:14; 384:15; 385:11; 407:1, 11,  
 12, 18; 409:18; 410:19; 416:1  
 laboratories [1] 77:14  
 lack [9] 34:17; 41:3; 186:14; 223:21;  
 232:5; 267:6; 276:1; 399:12; 412:15  
 ladies [6] 11:15; 14:1; 32:19; 130:16;  
 153:4; 178:16  
 laid [7] 225:19; 231:3; 237:14; 246:11;  
 247:14; 406:5, 19

language [1] 394:22  
 large [36] 10:17; 12:20; 13:3; 21:10;  
 26:22; 29:2; 102:3, 8; 105:17; 108:5;  
 134:17, 21; 142:5, 8; 144:13, 17; 151:19;  
 153:18; 155:16; 161:4; 177:16; 185:11,  
 21; 239:11; 240:6; 290:6; 298:4; 317:17;  
 318:20; 335:18; 369:19; 379:6; 387:17;  
 389:6,  
 13, 22  
 largely [6] 17:13; 23:6; 26:17; 78:4;  
 182:21; 310:4  
 larger [3] 44:17; 92:11; 254:16  
 largest [1] 163:5  
 Larry [1] 4:9  
 last [15] 50:17; 51:5; 81:18; 84:7; 91:19;  
 99:15; 116:7; 148:6; 194:14; 198:22;  
 223:2; 250:13; 271:18; 286:13; 362:2  
 late [2] 64:10; 103:18  
 latitudes [1] 303:5  
 laughter [4] 222:5; 231:12; 236:12; 356:11  
 launch [1] 198:8  
 laundry [1] 159:12  
 lay [1] 237:10  
 LB [1] 99:1  
 lead [7] 82:15; 83:18, 19; 84:5; 114:3, 4  
 leading [1] 114:2  
 leads [2] 53:15; 286:21  
 leaning [1] 332:9  
 leap [2] 314:9; 336:22  
 learn [1] 106:20  
 learning [3] 172:7; 211:7; 215:10  
 leave [7] 84:14; 105:22; 117:4; 299:12;  
 391:3; 411:21; 416:7  
 leaves [1] 295:3  
 left-hand [1] 171:3  
 Lemuel [1] 8:21  
 length [1] 16:5  
 lengths [1] 97:2  
 lesser [2] 42:12; 59:8  
 lethal [6] 128:7; 366:10; 370:17; 371:7,  
 14; 379:8  
 lethargy [1] 410:13  
 letters [1] 407:2  
 level [29] 25:22; 26:19; 35:10; 56:6; 58:5,  
 21; 59:8; 88:12; 121:13; 240:14; 242:16;  
 259:4; 265:2; 266:1, 2; 276:17; 279:13,  
 16, 18, 22; 294:10; 305:11, 22; 309:20;  
 310:3; 315:2; 359:15; 398:2; 404:2  
 Levels [1] 315:1  
 levels [19] 68:7; 70:18; 74:5; 95:6; 103:4;  
 127:2; 132:17; 228:1, 18; 229:8; 264:20;  
 265:6, 11; 279:6; 305:10, 20; 311:21;  
 314:21; 361:6  
 liberties [1] 331:11  
 liberty [1] 329:15  
 lie [1] 76:20  
 lies [1] 121:14  
 life [32] 7:9; 58:22; 100:10, 20, 21; 101:1;  
 102:12, 17; 123:16; 131:3; 145:8, 15;  
 146:1, 3, 7, 20; 147:1, 4; 152:17; 215:17;  
 219:22; 265:1; 272:7; 306:13; 308:7;  
 310:4; 326:1, 14; 338:11; 375:12; 391:8  
 life-threatening [1] 4:18  
 Lifestyle [1] 394:16  
 light [3] 17:8; 129:16; 292:7  
 lightheadedness [1] 147:22  
 liked [2] 227:5; 325:7  
 likelihood [3] 245:3; 363:22; 396:16  
 limit [6] 11:2; 178:18; 188:3; 219:6; 385:3;  
 388:6  
 limitation [1] 389:9

limitations [3] 285:3; 300:19  
 limited [13] 14:19; 18:19; 21:16; 34:18;  
 132:2; 184:13; 187:8; 190:4; 195:2, 20;  
 362:22; 390:17; 410:1  
 limiting [1] 394:16  
 limits [4] 160:4; 164:20; 264:4; 301:3  
 LINDENFELD [47] 78:15, 21; 79:14; 80:3,  
 15, 19; 81:18; 82:2, 9; 83:7, 16; 85:9;  
 117:8; 259:17; 260:7; 267:19; 268:7, 19;  
 269:1, 5, 8, 15, 19, 21; 270:12, 17; 271:4,  
 8, 15, 18; 277:12, 14; 278:3; 321:21;  
 332:17; 342:15; 351:8; 358:15; 364:18;  
 373:8; 379:2; 384:3; 390:9; 403:14; 406:8;  
 416:8; 420:9  
 Lindenfeld [2] 267:18; 269:16  
 line [19] 48:22; 51:1; 53:21; 65:13; 77:1;  
 81:6; 82:22; 178:3; 203:16, 17; 205:14;  
 206:12; 216:4; 246:7; 257:3; 268:17;  
 294:17; 348:10  
 linear [4] 45:10; 51:19; 141:2; 241:18  
 lines [4] 50:22; 72:1; 251:21  
 linkage [1] 33:11  
 linked [1] 65:3  
 Lipicky [9] 11:14; 14:1; 32:18; 130:16;  
 153:3, 13; 178:15; 220:10; 253:14  
 list [13] 41:6; 43:1, 4; 54:12, 19; 86:14;  
 87:4; 90:21; 91:1, 6; 159:12; 172:2;  
 177:10  
 Listed [2] 155:6; 169:13  
 listed [7] 18:18; 19:16; 34:18; 156:12;  
 161:10; 165:4; 395:17  
 Listen [1] 243:18  
 listen [2] 243:19; 389:6  
 listing [1] 288:21  
 lists [2] 19:19; 108:1  
 literally [3] 159:21; 388:10; 389:4  
 literature [6] 5:1, 4; 179:19; 184:15, 20;  
 378:5  
 liver [1] 357:6  
 lives [2] 27:22; 391:20  
 lo [1] 92:10  
 loading [1] 264:13  
 local [4] 176:1; 199:17; 271:17; 413:2  
 Locarin [2] 139:3; 140:17  
 log [6] 241:7, 8, 10, 14, 18; 250:10  
 logic [2] 355:1; 385:17  
 logical [4] 101:16; 114:1; 153:9; 310:22  
 logically [1] 299:1  
 logistics [1] 10:19  
 long-term [5] 161:15; 163:5; 169:22;  
 175:13; 327:9  
 longest [1] 97:10  
 longstanding [1] 30:12  
 looks [26] 55:20; 72:3; 79:6; 81:7; 125:8;  
 157:17; 187:15; 188:7; 210:9; 238:3, 5, 6;  
 242:12; 257:11, 15, 18; 262:16; 273:3;  
 280:19; 361:7; 364:3, 5; 380:14; 381:5;  
 385:3; 405:10  
 loops [2] 66:8; 67:7  
 loses [1] 304:4  
 loss [4] 18:12, 15; 25:19; 195:16  
 lost [1] 182:21  
 lots [8] 52:12; 106:19; 250:14, 15; 309:21;  
 329:1; 359:9; 396:21  
 Lou [1] 126:22  
 love [2] 112:19; 419:19  
 low [33] 40:16; 41:2; 45:16; 46:21; 47:4;  
 156:2; 179:2; 186:17, 18; 188:1, 8; 189:8;  
 192:10; 210:7; 217:14; 218:3; 294:3;  
 302:17; 305:17; 321:16; 323:12; 351:1;  
 357:6; 361:13; 362:10; 369:8, 22; 372:10;

373:2, 3, 9; 386:20  
 lower [27] 46:19; 136:20; 139:16; 155:2;  
 211:2, 10; 212:3; 217:1; 261:1; 262:5;  
 265:10, 11; 266:1, 2; 268:17; 276:13;  
 282:13; 292:17, 22; 293:11; 317:18;  
 323:8, 20; 361:6; 364:20; 378:11; 421:22  
 lowered [1] 218:20  
 lowering [1] 174:7  
 lowest [7] 58:21; 71:18; 72:11; 74:9;  
 244:9; 362:13  
 Loyd [1] 239:3  
 lukewarm [2] 329:11; 335:15  
 lump [3] 54:22; 91:13; 361:22  
 lumped [1] 366:17  
 lunch [3] 197:6, 12; 198:5  
 LV [15] 154:8; 158:13; 159:7, 14; 161:6;  
 192:3, 4, 15; 193:5; 213:17; 348:8; 350:6,  
 14; 351:3; 385:6  
 LVEF [1] 48:3  
 LVH [1] 347:1

---

- M -

---

macro [2] 22:17, 21  
 magnitude [6] 35:8; 42:1; 91:12; 101:11;  
 105:19; 116:18  
 main [7] 46:6; 64:20; 68:13; 90:19;  
 165:12; 199:16; 256:3  
 mainly [1] 199:16  
 mainstay [1] 19:17  
 maintain [4] 132:17; 310:17; 328:3; 411:4  
 maintained [7] 148:18; 183:16; 209:10;  
 249:5; 266:2; 304:17; 410:22  
 Maintaining [1] 152:14  
 maintaining [8] 12:14; 69:2; 135:19;  
 140:8; 143:2; 145:10; 265:10; 329:19  
 major [7] 11:4; 99:4; 357:4; 359:14, 17,  
 19; 395:19  
 majority [6] 20:12; 21:2; 35:6; 36:19;  
 139:20; 301:13  
 male [3] 5:19; 137:3; 167:14  
 males [5] 32:7; 95:20; 96:1; 143:4; 220:4  
 malignant [2] 372:13; 387:22  
 manage [2] 96:18; 294:1  
 managed [3] 7:5; 292:14; 294:4  
 management [3] 14:18; 18:9; 97:21  
 mandate [2] 403:3; 418:4  
 mandated [1] 411:9  
 mandatory [2] 402:4; 420:21  
 maneuvers [1] 407:11  
 manifests [1] 6:9  
 map [3] 53:10; 72:8; 88:16  
 margin [5] 53:14; 54:9; 84:8, 17; 302:16  
 marked [1] 47:6  
 markedly [5] 189:10; 378:6, 9; 380:11, 14  
 markers [1] 288:6  
 market [1] 6:17  
 marketed [3] 210:8; 299:18; 300:18  
 marketplace [1] 126:15  
 MARSHANT [14] 82:12; 83:10, 13; 85:14;  
 293:2, 12; 294:5; 296:7, 10; 304:15;  
 305:1, 6; 323:14, 22  
 Marshant [3] 82:12; 293:1; 304:14  
 Marv [7] 216:16; 309:19; 335:2, 345:5;  
 346:5; 350:15; 391:12  
 Marvin [11] 8:15; 286:19; 289:6; 320:21;  
 322:15; 329:12; 339:17; 358:6; 365:15;  
 377:12; 383:3  
 matched [1] 163:22  
 matching [1] 143:21  
 material [5] 141:14; 142:22; 146:4;

198:11; 233:11  
 math [1] 286:3  
 matter [11] 26:13; 60:15; 83:19; 115:5;  
 116:1, 2; 130:1; 197:12; 207:11; 281:5;  
 423:11  
 matters [1] 8:22  
 max [2] 69:7; 71:13  
 maximal [1] 42:2  
 maximally [1] 265:17  
 maximum [2] 213:18; 265:16  
 mayhem [2] 367:8; 370:8  
 meaning [3] 27:18; 325:19; 387:18  
 meaningful [2] 87:17; 137:11  
 meaningless [1] 331:3  
 means [10] 29:13; 41:22; 115:7; 187:1;  
 203:2; 237:21; 273:15; 309:8; 383:16, 17  
 meant [7] 222:18; 272:13; 273:5; 327:21;  
 379:20; 392:15; 394:7  
 measurable [1] 195:21  
 measure [12] 18:5; 56:8; 57:9; 82:17;  
 83:5; 97:2; 135:4; 170:1; 305:4, 9; 368:16;  
 403:1  
 measured [11] 57:7; 81:20; 82:3, 4, 13;  
 83:12, 14; 85:11; 176:9; 403:4; 413:2  
 measurement [3] 77:15; 133:5; 402:20  
 measurements [3] 44:3; 306:21; 336:4  
 measures [2] 145:7; 170:10  
 measuring [1] 83:15  
 mechanics [1] 82:7  
 mechanism [4] 74:17; 95:9; 123:20;  
 396:20  
 mechanisms [1] 396:13  
 mechanistic [1] 224:4  
 median [5] 32:1; 79:17; 209:3, 6, 10  
 mediated [2] 182:1; 183:9  
 medical [9] 4:22; 76:6; 78:6; 149:18;  
 398:18; 405:14; 406:11; 410:8; 421:7  
 medication [5] 108:9; 137:16; 176:15;  
 177:17; 298:10  
 medications [9] 66:6; 108:1, 3; 109:21;  
 117:20; 137:13; 176:18; 177:18; 272:17  
 medicine [6] 27:13; 177:19, 22; 300:2;  
 330:19; 409:11  
 medicines [1] 177:22  
 meds [2] 110:1; 175:9  
 meeting [5] 8:5, 6, 8, 12; 134:19  
 meetings [1] 393:2  
 MEMBER [1] 61:21  
 Members [1] 130:16  
 members [10] 6:20; 11:6, 14; 14:1; 32:18;  
 121:7; 153:4; 178:16; 313:15; 352:14  
 memorized [1] 98:9  
 memory [1] 246:22  
 men [5] 44:11, 21; 78:18; 79:9; 220:5  
 mentally [2] 240:9; 241:22  
 mention [5] 157:7; 185:11; 246:19;  
 398:22; 415:15  
 mentioned [14] 18:22; 79:8; 88:22; 89:1;  
 163:20; 165:4; 187:17; 225:21; 226:2;  
 259:3; 283:4; 297:21; 369:20; 420:15  
 mentioning [1] 362:2  
 merge [1] 92:17  
 message [2] 374:9; 394:9  
 meta [1] 189:5  
 metabolic [6] 40:11; 42:3, 9; 103:10;  
 118:9; 178:7  
 Metabolism [1] 40:13  
 metabolism [8] 34:8; 41:1, 3, 11; 43:13;  
 52:7; 92:13; 94:14  
 metabolites [1] 40:15  
 Metforman [1] 90:17

method [5] 33:18; 37:4; 138:21; 163:19;  
 331:4  
 methods [1] 409:21  
 meticulously [1] 296:19  
 MI [23] 159:9, 15, 19; 160:3; 162:6, 10,  
 12, 16; 164:18; 165:14; 172:19; 180:11;  
 181:15, 19; 190:22; 191:20; 192:14;  
 215:8; 226:14, 17, 22; 227:5; 350:19  
 Mibefradil [3] 6:20; 90:10, 13  
 micro [5] 133:8, 9, 10; 134:12  
 microgram [25] 49:21; 70:7; 136:15, 22;  
 139:11; 141:7, 17; 142:15, 20; 143:9;  
 144:7, 19; 147:5; 149:1; 150:21; 151:10,  
 18; 152:10; 202:8; 203:15, 16, 17, 22;  
 365:3; 367:15  
 micrograms [23] 46:18; 47:5; 48:1, 99:5;  
 155:2; 158:17; 163:11; 165:20; 168:16;  
 206:11; 211:2; 212:4, 8; 213:18; 228:8;  
 229:5; 247:6; 248:21; 253:8; 265:7; 365:2;  
 377:2  
 micron [1] 134:5  
 microphone [2] 4:8; 228:20  
 middle [6] 43:4; 46:4; 47:6; 60:4; 74:9;  
 375:9  
 midnight [1] 115:14  
 mig [1] 323:16  
 mike [1] 228:13  
 mild [1] 137:15  
 milligram [6] 136:16; 227:19; 228:2;  
 229:5; 367:15; 400:10  
 milligrams [4] 24:6; 221:20; 265:7; 407:15  
 milliliter [2] 49:17; 133:11  
 milliliters [2] 35:18; 133:12  
 million [3] 14:21; 16:1; 232:10  
 millisecond [2] 44:20; 219:2  
 milliseconds [6] 49:12, 16; 50:12; 133:17;  
 268:18; 279:22  
 mills [1] 103:1  
 Milton [1] 8:20  
 mind [7] 111:20; 126:1; 128:11; 241:13;  
 299:3; 341:3; 397:9  
 minimal [4] 27:20; 97:8; 121:9; 310:9  
 minimize [1] 125:3  
 minimized [5] 168:22; 169:2; 184:12;  
 196:10  
 minimizes [1] 174:10  
 minimum [3] 239:14, 17; 240:6  
 minor [4] 39:1; 40:13; 73:9; 114:16  
 minus [4] 98:15; 112:5; 118:21, 22  
 minute [7] 35:18; 92:2; 103:1; 133:11, 12;  
 178:18; 185:11  
 minutes [4] 129:21; 333:9, 10; 419:12  
 mirror [1] 366:19  
 mirroring [1] 265:2  
 misleading [2] 77:15; 402:1  
 misreading [1] 206:10  
 miss [2] 210:19; 271:6  
 missed [2] 127:1; 213:14  
 missing [4] 116:5; 148:5; 188:6; 296:3  
 mistake [1] 342:1  
 mixed [3] 109:16; 149:7; 253:14  
 mixture [2] 146:9; 255:6  
 mixup [1] 407:14  
 mixups [2] 407:20, 22  
 mode [5] 71:22; 255:7; 288:10; 289:7;  
 290:2  
 modeling [1] 109:16  
 models [1] 250:11  
 moderate [5] 36:12; 137:15; 192:4, 8;  
 357:6  
 moderately [2] 192:15; 395:12



modestly [1] 124:16  
 modification [3] 35:16; 194:15; 330:14  
 modified [1] 163:12  
 modify [1] 329:15  
 moment [4] 35:13; 39:15; 221:19; 409:16  
 noney [4] 107:2, 3, 12, 14  
 monitor [10] 57:18; 62:13; 65:1, 6; 311:19;  
 368:11; 399:13, 16, 17  
 monitored [4] 84:2; 136:4; 311:10; 370:1  
 monitoring [9] 46:1; 58:7; 65:5; 132:13;  
 169:4; 305:22; 360:16; 379:14; 404:4  
 monotone [1] 241:12  
 month [25] 28:21; 76:10; 139:4, 6; 140:7;  
 146:2; 147:3, 12; 187:5; 209:7, 12;  
 239:13; 241:4, 6; 248:15, 16; 268:10;  
 269:6, 9, 11; 279:2; 280:21; 326:13;  
 336:6, 11  
 months [47] 27:18; 31:13, 14; 50:21; 64:2;  
 135:14; 137:20; 138:2; 139:2, 8; 140:9,  
 18, 21; 141:4, 6, 18; 142:15; 144:5, 20;  
 147:11; 181:6; 204:7, 17; 205:3; 207:1, 9,  
 19, 21; 208:2; 209:17, 18; 241:3, 17;  
 244:20, 22; 263:19; 269:12, 14; 270:9;  
 278:20; 280:7, 20; 294:7; 302:21; 336:7,  
 8; 422:15  
 moot [3] 239:8; 240:22; 242:1  
 moral [1] 408:9  
 morbidity [3] 21:11; 169:21; 170:9  
 morning [7] 11:10; 129:17; 132:1; 136:8;  
 153:5; 168:19; 374:6  
 morphology [1] 82:19  
 mortalities [2] 159:18; 370:22  
 mostly [3] 153:16; 219:8; 335:16  
 motion [1] 158:14  
 motivate [1] 419:7  
 motivation [1] 160:19  
 nove [12] 11:7; 32:12; 96:16; 154:12;  
 265:15; 303:22; 307:22; 311:3; 319:16;  
 324:9; 366:16; 374:12  
 moving [2] 148:10, 12  
 Moyer [1] 8:21  
 multicenter [1] 26:22  
 multiform [3] 122:6, 12, 18  
 multiple [6] 45:11; 117:20; 145:12;  
 242:10; 336:4; 351:13  
 multiplicative [2] 118:3, 6  
 multiply [1] 98:15  
 multivariable [1] 117:18  
 multivaried [4] 109:18; 123:16; 167:17;  
 168:3  
 myocardial [4] 132:6; 159:6; 190:12;  
 192:2  
 myself [5] 56:20; 98:6; 170:16; 211:10;  
 382:21  
 mystery [1] 364:11

---

- N -

---

naive [1] 399:3  
 naivete [1] 399:4  
 name [3] 4:9; 11:10; 12:2  
 namely [2] 292:16; 348:7  
 names [1] 29:20  
 nanogram [1] 49:17  
 narrate [1] 171:1  
 narrow [4] 54:9; 160:4; 285:2; 302:16  
 natural [2] 241:9; 258:4  
 nature [3] 306:8; 345:11; 346:10  
 nd [2] 188:9; 341:3  
 needs [8] 54:13; 76:15; 217:19; 228:12;  
 358:12; 360:4, 13; 403:14

negative [4] 47:18; 48:14; 88:5; 232:14  
 negligible [5] 34:8, 9; 39:10; 40:17, 20  
 negotiations [1] 281:20  
 neo [1] 162:1  
 neocard [1] 384:20  
 nephric [2] 75:7; 360:5  
 nephron [1] 67:3  
 nervous [1] 282:14  
 net [1] 202:20  
 neurochord [1] 137:5  
 neutral [5] 190:17, 18; 191:9, 13; 193:15  
 newly [1] 23:13  
 news [1] 371:21  
 nice [13] 65:13; 107:17; 120:11; 232:3;  
 236:6; 254:17; 279:13; 417:18, 20, 21;  
 420:2, 4, 6  
 NICHOLS [1] 228:22  
 Nichols [2] 228:11; 279:8  
 NIH [1] 24:13  
 nine [3] 144:3; 255:8; 263:17  
 Ninety [1] 137:7  
 nitrates [1] 118:21  
 Nobody [1] 327:5  
 nobody [16] 60:13; 98:12; 127:18;  
 221:22; 233:8; 294:20, 21, 22; 327:1;  
 329:2; 337:17; 338:13; 349:10; 379:10,  
 13, 21  
 nodding [1] 57:4  
 nodes [1] 274:19  
 nods [1] 64:4  
 nomagrams [1] 404:18  
 nominal [6] 141:1, 4, 9, 19; 144:20;  
 147:18  
 nomogram [1] 76:19  
 non-AF [1] 172:20  
 non-answerable [1] 349:19  
 non-cardiac [2] 13:6; 183:22  
 non-clinical [1] 12:1  
 non-compliance [1] 304:11  
 non-issue [1] 90:1  
 non-life [1] 7:4  
 non-linear [1] 109:15  
 non-philosophical [1] 311:4  
 non-proarrhythmic [2] 375:21; 378:1  
 non-proportionality [1] 250:8  
 non-recommended [1] 396:16  
 non-renal [16] 39:1; 41:15; 42:4, 6; 52:6,  
 10; 73:9, 11, 16, 22; 74:4, 9, 14; 75:8;  
 95:21; 96:4  
 non-significant [1] 140:18  
 Nonpharmacologic [1] 19:7  
 nonpharmacologic [1] 19:14  
 noon [1] 115:15  
 normally [1] 73:9  
 nosology [1] 29:18  
 Note [1] 133:4  
 note [2] 49:18; 135:3  
 noted [3] 10:10; 43:21; 79:10  
 noticeable [2] 148:19; 310:10  
 noticed [1] 80:5  
 noting [1] 139:3  
 notion [5] 221:9, 11; 235:21; 243:2;  
 355:13  
 notwithstanding [1] 39:11  
 novel [3] 60:11, 18; 399:19  
 nuances [1] 68:2  
 null [1] 262:19  
 numbers [28] 15:12, 16; 66:6; 79:12;  
 105:17; 113:17; 116:11; 119:17, 19, 22;  
 136:19; 139:16; 186:11; 204:3, 5; 205:15;  
 216:8; 227:10; 244:21; 248:9; 251:2;

254:19; 263:3; 268:1; 322:6; 323:11, 13,  
 20  
 numerator [1] 290:17  
 numerical [3] 169:16; 238:6; 248:3  
 numerous [4] 313:20; 335:19; 336:19;  
 379:18  
 nurses [2] 77:11; 176:10

---

- O -

---

o'clock [1] 115:14  
 object [2] 115:6; 355:19  
 objectively [2] 9:7, 20  
 obliged [1] 407:17  
 observation [3] 148:6; 280:4; 371:2  
 observational [1] 115:9  
 observations [1] 279:4  
 observe [1] 166:3  
 observed [10] 46:11; 143:15; 147:11;  
 148:17; 165:11; 169:17; 170:5; 182:7;  
 183:1; 356:20  
 obtained [6] 8:17; 46:2; 92:10; 157:16;  
 186:14; 211:7  
 obtains [1] 158:2  
 obviate [1] 305:21  
 obvious [17] 29:5; 75:4; 104:15; 181:20;  
 182:2; 185:4; 189:9; 222:15; 227:21;  
 232:17, 18; 321:1; 337:8, 15; 338:19;  
 388:13, 22  
 Obviously [3] 111:16; 159:1; 390:4  
 obviously [18] 17:2; 22:11; 71:19; 73:10;  
 116:14; 126:15; 158:3; 168:1; 187:8;  
 198:16; 243:1; 273:7; 299:8; 318:19;  
 345:6; 349:1; 384:11; 408:9  
 occasional [2] 391:6; 393:20  
 occasionally [2] 318:2, 10  
 occur [11] 34:13; 35:3; 36:3; 42:2; 53:11;  
 63:5; 65:19; 74:18; 76:16; 122:16; 367:6  
 occurred [10] 60:3; 62:1; 71:9; 136:13;  
 167:12; 168:14; 208:7; 269:4; 402:7;  
 408:1  
 occurrence [3] 168:21; 177:6; 196:9  
 occurring [3] 169:15; 371:14; 402:10  
 occurs [6] 35:4; 43:11; 49:14; 50:6; 122:1,  
 2  
 odd [1] 102:19  
 odds [1] 366:9  
 offer [8] 14:7; 104:1; 178:20; 179:1;  
 184:5; 188:15; 211:21; 212:9  
 offering [2] 14:3; 27:12  
 office [1] 8:18  
 officer [1] 10:2  
 offset [1] 17:18  
 Oh [1] 400:5  
 Okay [34] 32:11; 57:3; 61:20; 75:21;  
 88:20; 102:15; 103:2; 119:3; 129:10;  
 217:13; 219:19; 249:6; 267:17; 269:15;  
 271:8; 277:11; 292:4; 307:21; 322:20;  
 324:7; 328:19; 335:17; 339:14; 347:10;  
 348:3; 354:17; 369:15; 377:8; 396:8, 9;  
 400:21; 413:15;  
 415:17; 423:8  
 okay [24] 53:3; 89:16; 104:5; 109:2;  
 202:1; 213:4; 231:8; 235:5; 255:13;  
 258:16; 299:2; 301:19; 302:10; 321:5;  
 338:8, 21; 347:9; 356:14; 359:15; 365:21;  
 394:5; 398:12; 410:2; 414:18  
 old [6] 60:6; 175:22; 272:15; 275:5, 9, 19  
 older [2] 15:2; 347:1  
 olds [2] 275:3  
 omnibus [2] 241:14, 19

## - P -

ones [12] 27:8; 57:20; 74:8; 87:3; 90:19;  
114:14; 162:1; 222:15; 253:10, 12; 354:3;  
357:4  
onset [4] 5:16; 17:18; 18:4; 29:10  
onward [1] 210:22  
operative [1] 394:7  
opinion [16] 26:6, 13, 18; 90:11; 112:19;  
236:1; 298:13; 317:5; 320:6; 334:22;  
341:6; 354:10; 381:1; 384:10, 16; 385:15  
opinions [1] 277:2  
opportunity [6] 7:14; 11:17; 118:2; 150:6;  
166:3; 367:21  
opposed [9] 79:9; 92:18; 118:14; 235:17;  
254:20; 256:11, 21; 327:7; 355:21  
opposite [2] 334:11; 346:12  
option [7] 22:5; 24:21, 22; 25:11; 195:8;  
231:19; 306:10  
options [13] 14:10, 18; 18:9, 17; 19:6, 14;  
21:14; 194:19; 195:1, 18; 232:10; 288:2;  
322:17  
Oral [1] 91:19  
oral [10] 5:20; 13:5; 92:6, 8, 18, 22; 93:1;  
131:12, 15  
orally [1] 92:12  
orchestrate [1] 97:21  
order [15] 21:19; 33:6; 106:17; 132:16;  
218:14; 244:17; 247:10; 257:8; 273:13;  
286:4; 302:2; 314:9; 356:2, 3; 403:17  
ordered [1] 244:8  
ordinarily [3] 28:7, 8; 274:8  
organ [2] 25:6; 357:2  
Organic [1] 90:16  
organic [17] 37:8, 9, 11, 16, 18; 38:4, 7,  
10, 11, 17; 39:19, 21; 40:1; 41:20; 67:3;  
88:15; 118:13  
oriented [2] 319:8; 374:12  
original [2] 159:1; 241:2  
ought [12] 58:12; 59:2; 68:18; 100:22;  
119:1; 307:22; 311:2; 316:12; 360:15;  
362:22; 399:11; 419:11  
ours [1] 412:10  
out-patient [3] 166:19; 361:11; 403:20  
outcome [4] 26:21; 138:9; 192:18; 260:16  
outcomes [2] 146:7; 380:9  
outlined [1] 324:22  
outpatient [4] 286:16; 287:10; 292:2;  
302:13  
output [1] 315:12  
outputs [1] 386:20  
outs [1] 183:10  
outside [1] 406:4  
outweigh [2] 318:5; 389:16  
outweighed [1] 309:1  
outweighs [2] 392:12; 394:20  
Overall [3] 137:9; 144:6; 160:6  
overall [18] 12:8; 35:1; 39:10; 73:3; 74:11,  
12; 138:9; 140:17; 149:3; 163:3; 164:21;  
173:13; 182:7; 184:7; 213:2; 240:14;  
292:9; 293:21  
overdosed [1] 367:10  
overdosing [1] 282:16  
overestimate [1] 400:15  
overlap [2] 261:6; 282:3  
overlaps [2] 262:19; 263:2  
overseeing [1] 406:12  
oversensitive [1] 240:19  
oversimplification [1] 84:22  
overview [1] 14:4  
overwhelmed [1] 341:14  
overwhelming [2] 232:14; 253:1  
owns [1] 9:22

P-glycoprotein [13] 34:9; 37:10, 16; 39:6,  
7, 9, 12, 17; 40:5, 6; 103:8; 105:1  
p.m. [3] 197:11; 198:2; 423:10  
pack [1] 375:9  
package [9] 75:5, 11; 127:7; 231:14;  
250:20; 251:22; 252:4; 381:21; 417:19  
packages [1] 374:1  
Packer [1] 8:21  
packet [2] 80:5; 117:15  
PAF [10] 223:15, 21; 225:18; 236:9;  
253:13; 376:22; 416:17, 21, 22; 417:2  
Page [1] 155:7  
page [8] 134:1; 142:21; 154:18; 156:21;  
169:11, 18; 172:1; 175:10  
pages [3] 141:13; 146:5; 157:19  
pain [1] 147:22  
painful [1] 7:3  
palpitation [4] 309:16, 18; 391:6; 393:21  
palpitations [4] 17:15; 99:9; 148:1, 20  
panel [25] 48:21; 61:5; 109:7; 128:18;  
162:8; 222:8; 296:22; 307:13; 309:21;  
311:3; 313:15; 314:4; 324:8, 15; 329:10;  
344:7; 345:4; 351:10; 352:14; 354:7;  
363:14; 409:8; 410:14; 413:7; 415:4  
paper [1] 239:12  
papers [1] 287:12  
paradigm [1] 75:17  
paragraph [1] 241:4  
parallel [3] 135:15; 241:15; 255:22  
parameters [1] 109:22  
paraphrased [1] 54:14  
parentheses [1] 319:22  
parenthetically [1] 94:10  
paretral [1] 20:2  
Parklawn [1] 8:19  
paroxetine [1] 420:16  
paroxysma [1] 31:12  
Paroxysmal [1] 17:10  
paroxysmal [12] 17:6; 20:4; 223:10;  
224:4, 9; 225:8; 236:14; 253:13, 16;  
254:2, 4; 343:13  
Part [1] 41:10  
part [43] 8:5; 41:11; 50:5; 51:22; 56:9, 16;  
113:7, 8; 126:1, 9; 128:13, 17; 192:21;  
221:18; 222:6, 10; 314:14; 315:4; 329:14;  
332:12, 14; 334:10, 11; 335:5, 12, 13, 16,  
18; 340:21; 341:6, 13, 15; 342:19; 343:10;  
344:15; 349:7; 374:2; 375:3;  
384:12; 395:11; 412:19; 419:5; 423:3  
participant [2] 9:6; 10:7  
participants [4] 8:9; 9:20; 10:8, 11  
participated [1] 9:9  
participating [1] 8:21  
participation [1] 9:7  
particulars [1] 256:11  
partly [2] 123:21; 395:10  
parts [4] 105:4; 131:20; 167:9; 240:15  
pass [1] 77:9  
passed [1] 199:15  
path [3] 25:16; 38:5; 121:14  
paths [1] 53:16  
pathway [14] 36:2; 37:9, 11, 18; 38:4;  
39:6; 40:13; 42:3, 17; 54:18; 88:11; 118:7,  
18  
pathways [1] 37:7  
Patients [13] 131:20; 132:5; 133:12;  
136:3, 6, 10, 14; 139:10; 147:5; 150:3;  
151:4; 159:13; 212:2  
pay [3] 24:16; 367:22; 400:13

paying [1] 407:21  
PD [1] 33:21  
peak [5] 34:13, 21; 57:13; 95:6; 108:21  
peaks [1] 95:13  
peer [1] 4:22  
pending [1] 385:10  
peoples [2] 165:13; 287:21  
perceived [1] 388:13  
percentage [9] 19:10; 21:5; 29:3; 145:21;  
147:2; 161:4; 224:6; 272:6; 322:2  
perception [2] 121:2; 145:14  
percutaneous [1] 317:22  
perfect [2] 307:5; 316:6  
perfectly [5] 310:22; 342:2; 359:11;  
366:18; 369:7  
performed [14] 38:18; 46:10; 48:1, 6;  
86:10, 11, 16; 161:3; 181:8; 182:4, 16;  
183:11; 193:19; 398:12  
performs [1] 37:5  
perfunct [1] 345:17  
period [22] 19:1; 29:5; 57:18; 58:11;  
100:14; 135:22; 190:8; 199:2, 3, 4, 7, 11,  
18; 200:13; 219:2; 268:12; 270:20;  
317:19; 334:19; 367:2, 5; 416:6  
periods [1] 28:11  
permanent [1] 30:11  
permit [2] 179:4; 186:5  
permute [1] 33:11  
perplexing [2] 223:22; 254:6  
persist [1] 30:20  
persistent [12] 30:1, 10, 12; 131:10;  
157:10; 179:20; 224:5; 225:1; 253:5, 16;  
254:3, 4  
persists [2] 100:12; 279:21  
person [5] 236:1; 254:1, 3; 279:17; 365:4  
personal [5] 26:6, 18; 27:12; 331:18;  
346:21  
personally [7] 9:15; 64:3; 308:20; 378:17;  
392:6; 406:8; 419:19  
perspective [6] 27:12; 119:10; 179:5;  
186:5; 209:15; 317:3  
perspectives [1] 178:13  
persuading [1] 405:1  
pertains [1] 219:11  
pertinent [5] 30:15; 221:2, 6; 286:6;  
414:11  
Pete [1] 234:7  
Peter [40] 8:16; 29:15; 61:8; 88:17;  
110:20; 112:19; 157:10; 223:7; 225:4;  
226:9; 234:20; 275:9; 276:1; 284:8; 285:6;  
286:13; 320:3, 20; 322:20; 324:8; 329:10;  
334:8; 335:19; 347:17; 348:13; 356:13;  
369:10; 370:8; 374:13; 392:2, 17; 393:17;  
394:10; 396:2, 18; 398:4; 411:1; 413:12;  
415:4; 417:16  
PF [1] 253:15  
Pfizer [6] 10:1; 11:12, 16; 12:4; 82:12;  
197:7  
PH [1] 37:13  
phagiatonia [1] 275:7  
Pharmacia [1] 10:1  
pharmacists [1] 77:11  
pharmacodynamic [12] 13:16; 33:20;  
46:8; 47:15; 50:3; 67:13; 99:13; 111:17;  
114:21; 218:15; 266:5; 279:12  
pharmacodynamics [7] 33:16; 80:4, 9;  
108:6; 113:5; 418:20, 21  
pharmacokinetic [24] 13:16; 33:19; 34:3;  
37:3; 38:9; 40:3; 42:15; 43:7; 44:1, 17;  
45:1; 46:7; 58:15; 66:14; 67:6, 13; 99:13;  
104:12, 18; 109:21; 114:20; 116:9; 126:5;

- 129:3  
 Pharmacokinetics [1] 418:19  
 pharmacokinetics [18] 33:16; 43:21; 44:13; 45:2, 10, 11, 16; 67:5; 68:3; 73:1; 76:13; 99:20; 107:22; 109:15, 17; 418:18, 2; 419:15  
 pharmacologic [3] 12:15; 89:18; 197:1  
 pharmacological [4] 150:12, 16; 203:1; 248:19  
 pharmacologically [9] 136:7; 150:6; 151:5; 179:12; 200:18; 201:1; 202:7, 18; 203:3  
 pharmacologist [1] 56:14  
 pharmacology [9] 32:16, 22; 33:6; 51:10; 165:19; 228:6, 9; 229:2; 283:5  
 pharmacy [1] 406:15  
 phase [26] 36:13; 38:8; 40:3; 42:14; 44:2, 18; 45:4, 21; 46:12; 92:16; 136:4, 12; 166:14; 200:4, 22; 202:4; 203:6; 207:7; 233:18; 360:18, 19, 21; 361:4; 366:2, 3  
 phases [2] 361:21; 397:19  
 phenomenon [1] 307:5  
 Phenotype [1] 356:22  
 phenotype [1] 356:22  
 physical [2] 146:15; 147:16  
 physician [12] 271:16; 326:2; 387:16; 389:15; 390:18; 391:16; 394:19; 406:9; 408:13, 14, 21, 22  
 Physicians [1] 399:19  
 physicians [16] 77:11; 83:9; 176:10; 224:16; 230:9; 232:21; 301:1; 305:13; 324:18; 392:10; 399:19; 400:2; 402:19; 403:10; 405:16; 410:10  
 physiological [1] 37:13  
 PIA [16] 278:16; 280:3, 17; 321:11; 332:5; 341:12; 351:6; 358:4; 372:12; 378:17; 384:1; 389:18; 402:18; 416:3, 22; 419:14  
 Pia [1] 278:15  
 pick [4] 87:16; 127:3; 245:11; 403:1  
 picked [3] 104:16, 18; 110:2  
 picture [2] 113:8; 120:12  
 piece [1] 351:20  
 pieces [1] 120:5  
 pin [1] 309:9  
 pink [1] 15:6  
 pivotal [9] 46:16; 154:3; 155:15; 157:3; 164:14; 187:3; 211:20; 252:4; 263:6  
 PK [12] 33:21; 108:6, 17; 110:19; 111:15; 113:6; 125:22; 126:18, 19, 20, 22; 127:14  
 PKs [1] 37:14  
 place [10] 179:5; 186:5, 12; 199:10; 256:6; 283:8; 284:5; 402:22; 407:1; 413:5  
 Placebo [2] 159:18; 319:21  
 placed [1] 210:13  
 placement [1] 27:9  
 plainly [2] 346:7; 422:4  
 planning [1] 328:2  
 plasma [25] 40:17; 44:3, 10; 46:11; 49:6; 51:19; 56:21; 57:15; 59:10; 65:7; 68:19; 94:3; 104:13; 115:19; 116:20, 22; 122:21; 279:13, 16, 18; 303:2, 4; 305:22; 364:4, 9  
 plateau [2] 63:12; 72:4  
 plateauing [2] 63:15; 69:22  
 plausibility [1] 146:21  
 play [2] 22:2; 218:22  
 plays [1] 22:11  
 please [2] 135:3; 170:22  
 please [13] 4:7; 85:19; 153:7; 203:12; 212:20; 213:10; 226:8; 259:1, 6; 262:3; 266:15; 272:13  
 plot [5] 69:7; 72:2; 119:10, 14; 120:8  
 plots [1] 159:18  
 plotted [2] 55:21; 119:11  
 plug [1] 115:21  
 plus [11] 43:13; 86:12; 122:8; 206:15; 263:22; 264:1; 268:3; 285:18; 303:16; 415:14  
 podium [1] 198:10  
 Point [1] 122:20  
 pointed [7] 6:8; 153:13, 18; 215:19; 329:21; 348:16; 359:6  
 pointing [2] 344:10; 355:20  
 points [18] 13:1; 122:8; 133:22; 165:10; 166:12; 173:18; 175:16; 184:3; 185:6; 196:8; 239:5; 244:16; 257:4; 278:9; 282:2; 325:19; 343:18; 388:16  
 poisoned [1] 391:8  
 poisons [1] 314:17  
 policy [2] 281:5; 403:17  
 poly-pharmacy [1] 418:11  
 polymorphic [2] 5:21; 132:9  
 polypharmacy [1] 370:15  
 pondering [1] 34:15  
 pool [5] 104:14; 121:7; 190:20; 323:14; 380:8  
 pooled [1] 156:22  
 pooling [2] 142:8, 11  
 poor [4] 56:13; 58:2; 77:7; 272:10  
 poorly [1] 347:3  
 popped [1] 106:15  
 pops [1] 109:3  
 populations [24] 143:18; 153:21; 159:20; 164:18, 20; 171:3, 15; 172:12, 19; 173:4; 185:3; 189:15; 190:1; 194:8; 223:22; 226:18; 267:21; 268:3; 331:13; 357:13; 383:14; 417:14; 421:14; 422:17  
 portion [2] 82:21; 98:3  
 posited [1] 66:18  
 position [2] 125:20; 342:2  
 positive [15] 37:13; 127:5; 134:14; 142:1; 144:21; 151:16; 239:6, 17, 21; 241:22; 252:6, 15, 16; 319:14, 18  
 positively [1] 320:8  
 positives [1] 342:4  
 possibilities [8] 233:13; 234:5; 299:7, 15; 300:5, 13; 301:2; 421:4  
 possibility [4] 38:8; 188:2; 266:18; 299:11  
 post-algorithm [2] 165:17; 215:21  
 post-infarction [3] 189:21; 191:5; 192:1  
 post-market [1] 418:4  
 post-marketing [2] 417:13; 418:7  
 post-MI [7] 162:10; 190:22; 290:4; 350:8, 13; 357:13, 18  
 post-op [1] 101:21  
 posterity [1] 232:1  
 potassium [4] 35:5; 65:16, 19; 66:22  
 potency [2] 40:18; 41:22  
 potent [5] 39:9; 41:7, 9; 52:4, 14  
 potential [25] 5:13; 8:11; 12:5; 13:11; 22:19; 36:2; 42:11; 54:19; 67:4; 76:13; 80:12; 86:3; 90:12; 105:1; 153:16; 225:16; 318:5; 334:21, 22; 361:20; 373:4; 377:20; 388:1; 390:12; 420:22  
 potentially [8] 4:18; 7:9; 92:13; 161:20; 320:16; 372:19; 385:9; 386:21  
 potentiating [1] 52:9  
 pounds [1] 98:10  
 power [2] 240:6; 350:22  
 powered [2] 145:8; 243:7  
 powerful [2] 341:10; 390:1  
 practical [4] 58:2; 61:20; 83:19; 208:22  
 practice [9] 25:15; 199:17; 258:4; 265:9; 271:17; 362:18; 373:11; 396:17; 409:10  
 practices [1] 27:13  
 Practitioners [1] 223:13  
 practitioners [2] 176:6; 223:13  
 PRATT [36] 153:3; 212:15, 19; 213:10, 15; 215:1; 216:20; 217:3, 11, 17, 22; 218:5; 219:13, 18, 20; 223:2; 224:20; 226:6; 227:12, 16; 228:4, 19; 267:9; 268:1; 278:6; 284:4; 286:13; 287:9; 288:13, 20; 289:1, 16; 290:10; 291:12; 303:9, 13  
 Pratt [18] 13:19; 84:20; 108:7; 132:1; 153:1; 180:9; 184:4; 185:15; 186:9; 211:5, 14; 212:10; 219:12; 279:7; 282:22; 286:11; 288:18; 298:5  
 pre [2] 165:17; 215:21  
 Pre-specified [1] 145:6  
 pre-specified [11] 134:19; 137:18; 140:6, 16; 141:10; 144:14; 150:20; 181:8; 252:8; 257:4; 336:1  
 pre-systemic [1] 34:6  
 precise [3] 112:20; 396:2, 3  
 precisely [3] 18:5, 21; 26:17  
 precision [6] 53:9; 111:13, 14; 113:18; 116:1; 128:2  
 preclude [1] 8:5  
 precluded [1] 251:12  
 predefined [1] 163:14  
 predict [8] 34:12; 50:16; 57:12; 94:19; 114:21; 185:22; 186:1; 311:18  
 predictable [3] 45:2, 11; 49:4  
 predictably [1] 35:9  
 predicted [1] 43:2  
 predicting [2] 315:4; 348:21  
 predictive [1] 311:9  
 predictor [2] 64:22; 68:17  
 predictors [3] 44:6; 168:4; 185:16  
 predicts [1] 41:3  
 predispose [2] 6:10; 293:15  
 predisposed [1] 143:22  
 predisposition [1] 312:2  
 predominantly [2] 137:3; 290:1  
 predominate [1] 17:16  
 preempt [1] 356:4  
 prefer [1] 352:15  
 preferred [1] 274:2  
 preliminary [3] 93:17, 22; 95:13  
 premature [1] 193:6  
 prematurely [1] 31:5  
 premise [1] 281:21  
 preparation [2] 360:20; 361:10  
 preparations [1] 100:12  
 prepared [2] 67:14; 417:7  
 prescribe [1] 298:20  
 prescribed [4] 20:18; 129:18; 189:12; 208:10  
 prescribing [3] 282:11; 372:15; 396:16  
 prescriptions [4] 20:11; 21:2, 6; 405:10  
 presence [10] 16:22; 88:8; 158:1; 171:20; 185:19; 194:9; 195:16; 287:17; 348:7; 352:3  
 present [21] 8:1; 11:17, 22; 12:12; 14:17; 19:8; 20:16; 21:13; 23:7; 25:10; 26:19; 27:4; 32:21; 61:15; 130:18; 131:1; 169:11, 12; 187:2; 193:10; 303:16  
 presentation [17] 11:3, 9, 21; 13:8, 9, 21; 32:13; 33:14; 79:21, 22; 105:4; 112:3; 130:12; 132:1; 153:2; 213:14; 283:15  
 presentations [3] 13:14; 67:18; 130:6  
 Presented [1] 161:21  
 presented [23] 11:5; 13:12; 117:14; 144:10; 152:5; 158:10; 159:17; 160:22;

164:10; 165:15; 170:2; 171:5; 186:9;  
198:20; 211:14; 253:9; 278:7; 283:2, 14;  
299:8; 302:10; 332:16; 360:2  
preservation [1] 181:5  
preserved [3] 48:21; 138:13; 263:4  
preside [1] 197:8  
President [1] 11:11  
pressing [1] 331:21  
pressure [3] 80:6, 16; 81:15  
presumably [4] 192:11; 210:8; 293:21;  
305:4  
presume [4] 41:8; 53:5; 54:21; 89:10  
presumed [2] 290:11, 13  
presuming [1] 333:12  
Pretty [1] 105:5  
pretty [33] 26:9; 32:12; 47:2; 52:21; 66:4;  
80:2; 90:21; 93:2; 100:11; 101:18; 109:2;  
172:6; 188:3; 214:6; 215:17; 246:3;  
272:22; 279:3; 284:14; 303:5, 10; 321:7;  
324:4; 333:2; 340:13; 351:3; 367:20;  
369:8, 22; 371:15; 378:7; 401:20; 419:6  
prevalent [3] 15:1; 139:20; 169:14  
prevent [4] 4:20; 5:7; 7:11; 412:21  
preventing [2] 6:6; 354:8  
prevention [3] 20:3, 7; 319:9  
prevents [2] 310:21; 344:8  
previous [8] 10:13; 63:9; 74:3; 154:13;  
163:22; 174:16; 189:14; 266:14  
previously [8] 9:2, 9; 41:18; 43:21;  
145:18; 158:7; 165:13; 172:13  
primarily [3] 38:1; 153:9; 280:19  
primary [25] 16:4, 8; 18:13, 15; 21:21;  
132:14; 135:17; 137:19; 138:19, 21;  
140:6; 141:15; 158:20; 159:16; 168:17;  
184:2; 198:18; 208:20; 224:9; 252:8;  
258:13; 317:13; 321:3; 325:7; 335:20  
prime [1] 314:21  
principal [2] 160:19; 168:20  
principles [1] 133:21  
Prior [1] 205:19  
prior [3] 166:1; 207:21; 253:6  
priori [1] 312:7  
Pritchard [1] 157:1  
PRKR [1] 47:17  
proarrhythmic [1] 5:5  
proarrhythmia [16] 153:15; 160:9; 165:3;  
168:6, 7, 18; 174:11; 184:3; 196:6; 293:8;  
348:19; 350:9, 11, 12; 354:12; 388:1  
proarrhythmias [1] 153:17  
proarrhythmic [18] 191:12; 192:10; 348:5,  
6; 372:16; 377:17, 21; 378:10, 12, 13;  
379:8, 14; 380:6, 13, 14, 21; 387:2;  
401:11  
probability [10] 50:20; 69:18; 84:10;  
119:11, 12; 120:8; 150:15; 203:13;  
204:13; 349:2  
probe [2] 37:17; 101:15  
problem [47] 14:5, 11, 18, 21; 16:9; 18:6,  
13; 19:4; 20:19; 21:9; 53:19; 54:12; 68:20;  
77:13; 96:20; 97:7, 8, 13; 114:22; 116:18;  
117:18; 124:5; 185:5; 186:16; 196:4;  
232:16; 242:17; 250:4; 256:2; 282:18;  
295:4; 296:9; 306:16; 312:14; 314:14;  
322:22; 323:5; 331:6; 347:6; 348:16;  
362:1; 373:15; 381:1; 387:18; 395:2;  
400:19; 412:10  
problems [12] 6:16; 16:13; 97:5; 111:14;  
112:22; 252:3; 275:4; 347:6; 361:20;  
372:8; 373:4, 6  
Procainamide [1] 184:22  
procainamide [2] 37:19; 399:1

proceed [1] 7:20  
process [3] 53:13; 55:2; 306:9  
produce [3] 249:7; 282:4; 346:3  
producing [1] 248:1  
products [3] 10:4, 6, 14  
profile [5] 220:14; 369:6; 370:7; 375:22;  
378:18  
program [25] 7:5; 12:3, 8; 33:6; 131:11,  
13, 15, 21; 133:22; 153:19; 154:16;  
167:12; 170:17; 172:8; 211:8; 230:7;  
242:10; 251:2; 299:7; 374:2, 10; 396:10;  
404:19, 21  
programs [1] 264:14  
projectors [1] 331:22  
projects [1] 9:12  
prolong [8] 16:5; 22:19; 58:10; 100:8;  
230:15; 247:16; 282:4; 313:1  
prolongating [1] 229:19  
prolongation [24] 56:4, 6; 57:12; 59:7;  
63:20; 68:12; 84:16; 121:5, 10, 13; 132:4;  
139:14; 153:13; 154:19; 155:13, 18;  
161:10; 263:16; 266:7; 268:17; 311:8;  
312:9; 314:20; 347:16  
prolongations [2] 143:21; 144:1  
prolonged [12] 6:1; 50:10; 56:2; 100:14;  
132:20; 133:1; 168:11; 268:11; 271:5;  
277:17; 304:22; 305:5  
prolonging [4] 29:5; 132:10; 133:20;  
381:19  
prolongs [1] 101:1  
prominent [2] 23:3; 378:14  
prominently [1] 182:8  
promising [1] 236:4  
pronounced [1] 147:14  
propranolol [1] 20:6  
proper [1] 406:12  
properly [4] 300:6; 372:13; 400:13;  
405:21  
properties [5] 12:10; 13:16; 105:16;  
231:3, 6  
proportion [11] 138:20; 139:7; 140:7;  
150:19; 151:9; 157:9; 199:21; 201:18;  
205:5; 210:3; 422:18  
proportional [1] 250:11  
proportionality [1] 250:4  
proportionately [2] 323:21; 324:6  
propose [4] 153:8; 297:12; 305:21; 417:9  
proposed [6] 75:22; 144:8; 152:11; 173:8;  
196:11; 216:10  
proposing [2] 267:4; 305:9  
proposition [1] 11:2  
Propranolol [3] 81:1, 5, 8  
propranolol [1] 80:14  
prospective [1] 36:21  
protection [1] 315:19  
protocol [17] 31:17; 59:7; 99:18; 207:22;  
208:8, 9; 209:13; 213:12; 237:14; 241:1,  
2; 243:3; 270:15; 271:12, 14; 403:3  
protocols [2] 201:15; 358:19  
provable [1] 391:19  
prove [3] 225:8; 235:22; 388:11  
provide [7] 27:1; 134:8; 145:9; 150:9;  
195:8; 197:1; 409:20  
provided [3] 326:13, 20; 387:13  
provides [2] 135:8; 224:13  
providing [3] 233:2, 3; 286:9  
provision [1] 300:17  
provoked [1] 350:12  
PSVT [5] 235:20; 236:4, 8; 253:14, 15  
psychological [2] 145:13; 147:17  
psychologically [1] 326:4

Public [3] 4:10, 12; 6:14  
public [7] 4:6; 7:17; 9:19; 19:1; 21:9;  
190:8; 408:4  
publications [1] 407:6  
published [2] 5:3; 194:15  
pull [1] 301:21  
pulmonary [3] 24:3, 7; 224:9  
pun [1] 207:11  
pure [3] 23:6; 191:4; 224:3  
purely [1] 340:18  
purposely [2] 220:21; 406:7  
purposes [2] 236:19; 237:2  
pushing [2] 277:10; 343:14  
puts [2] 229:7; 406:22  
putting [1] 231:13  
PVCs [1] 336:20

## - Q -

QD [1] 260:15  
QDC [1] 50:10  
QTc [41] 44:21; 49:4, 6, 9; 50:16, 18;  
51:1; 65:4; 68:12; 69:20; 78:16; 81:20;  
82:4; 83:9; 108:7; 119:5; 132:19; 133:1,  
15; 143:21, 22; 161:8; 168:3; 171:19;  
218:15, 21; 263:16; 266:6; 268:17;  
279:11, 13, 20; 298:6, 8; 303:15; 304:16,  
21;  
305:4, 10, 12, 21  
QTcs [1] 168:1  
QTs [6] 64:21; 122:22; 123:4; 300:6, 7;  
402:20  
quagmire [1] 411:20  
qualify [1] 382:18  
qualifying [1] 382:17  
quality [17] 93:8; 131:3; 145:7, 14; 146:1,  
3, 7, 20, 22; 147:1, 4; 152:17; 272:7;  
310:4; 325:22; 326:14; 344:1  
quantifiable [1] 40:17  
quantitative [1] 252:19  
quarter [1] 367:6  
quarters [2] 74:12; 367:3  
queried [3] 40:4; 42:14; 80:9  
questioning [1] 250:5  
questionnaire [1] 147:20  
quick [4] 31:22; 191:16; 286:3; 329:9  
Quickly [1] 303:12  
quickly [9] 63:4, 12; 81:3; 85:9; 100:13;  
117:8; 227:13; 279:3; 332:2  
quinidine [2] 97:6; 312:11  
quit [1] 56:12  
quote [2] 412:2, 3  
quoted [1] 346:20

## - R -

rack [1] 241:7  
radically [2] 298:13, 18  
raise [1] 255:3  
raised [6] 72:21; 92:12; 255:2, 4, 20;  
322:18  
raises [3] 93:5; 111:20; 274:22  
raising [3] 255:2; 333:12; 407:5  
Ralph [8] 8:16; 198:18; 237:5; 246:2;  
251:10; 255:1; 341:16; 390:2  
ran [1] 207:12  
randomization [3] 205:16; 216:15; 290:15  
randomized [33] 26:14; 46:17; 48:2, 7;  
133:7; 134:5; 135:14; 136:14, 22; 139:10;  
140:10; 143:9; 144:6; 146:6; 147:5; 150:7;  
152:10; 155:1; 157:11; 158:15; 163:7;  
172:17, 20; 173:1; 205:13, 22; 211:1;

215:3, 13; 217:15; 263:11; 264:2; 268:5  
 range [20] 46:22; 47:8, 11; 70:8, 15;  
 79:16; 87:22; 102:22; 106:3; 116:20;  
 157:18; 169:7; 180:3, 7; 306:14; 371:1, 4;  
 391:10; 393:14; 410:6  
 anges [1] 400:17  
 ranging [9] 16:21; 134:12; 135:13; 142:4;  
 144:22; 241:11; 253:5, 17; 265:14  
 rank [5] 241:8, 10, 14, 18; 250:11  
 rapid [3] 18:13; 34:22; 98:19  
 rarely [1] 185:7  
 rates [22] 18:13; 98:19; 99:3; 179:18;  
 180:2; 181:17; 182:3; 183:6; 184:5, 16;  
 193:17; 194:6; 270:16, 17; 272:9, 15, 22;  
 273:5; 288:5; 306:11, 13; 323:8  
 ratio [10] 85:5; 143:19; 173:11; 181:18;  
 182:12; 188:12; 190:21; 260:18; 284:16;  
 390:19  
 ration [1] 160:2  
 ratios [7] 142:17; 161:21; 186:12, 14;  
 189:20; 249:22; 250:1  
 Ray [21] 84:22; 110:5; 113:12; 115:3;  
 120:21; 124:14; 125:19; 232:4; 233:21;  
 298:22; 301:6; 344:10; 376:9; 381:7;  
 385:14; 400:22; 406:8; 409:12; 412:11;  
 415:22; 416:11  
 re-entrant [3] 22:17, 20, 21  
 reach [4] 232:4; 264:21; 299:9; 309:3  
 reaction [4] 230:11; 301:20; 398:16; 407:7  
 read [11] 172:3; 241:1; 242:6; 243:3;  
 288:16; 300:6; 330:4; 372:8; 382:16  
 readily [1] 102:9  
 reading [8] 30:20; 60:4; 175:8; 298:6, 7, 8;  
 300:7; 375:18  
 real [23] 63:17; 77:13; 97:13; 111:22;  
 175:19; 176:11; 187:14, 15; 207:10;  
 208:11; 215:17; 219:22; 236:4; 284:3;  
 327:8; 366:20; 369:4; 370:3; 372:6;  
 373:22; 375:12; 413:3; 419:16  
 realistic [1] 22:5  
 reality [2] 314:18; 324:20  
 realize [7] 24:7, 11, 17; 157:8; 165:16;  
 279:1; 407:15  
 realized [2] 170:17; 211:8  
 realizing [2] 24:8; 172:7  
 reason [33] 10:22; 16:8; 51:17; 59:2;  
 64:20; 85:12; 101:17; 111:11; 113:14, 19;  
 116:13, 17; 117:21; 161:6; 199:16;  
 209:22; 219:4, 5; 223:10; 232:6; 239:9,  
 19, 20; 283:21; 355:21; 363:5, 9; 364:15;  
 371:18; 385:21; 387:1; 399:5, 21  
 reasonable [14] 26:9; 30:6, 8; 37:12;  
 42:10; 103:4; 106:10; 230:13; 274:9;  
 300:13, 16; 340:1; 365:3; 389:9  
 reasonably [7] 79:13; 113:16; 329:18;  
 332:2; 349:2, 21; 407:21  
 reasoning [3] 293:19; 395:8; 396:7  
 reasons [16] 22:15, 17; 58:14; 128:3;  
 155:6; 183:10; 205:6; 207:2; 227:21;  
 256:3; 304:7; 315:10; 334:14; 379:19;  
 388:5; 420:1  
 reassurance [1] 289:15  
 reassure [1] 267:20  
 reassured [1] 112:13  
 reassuring [3] 164:22; 395:10, 12  
 recall [2] 377:1, 3  
 receive [4] 46:18; 77:4; 155:1; 418:11  
 received [23] 46:19; 47:5; 48:10; 86:12;  
 136:20, 22; 139:15; 155:2; 173:2; 210:10,  
 14, 15; 211:2, 18; 212:22; 214:2, 9; 217:7;  
 221:4; 260:4, 5; 336:14; 417:19

receives [1] 133:8  
 receiving [16] 38:10, 11; 40:6, 7; 42:18,  
 19; 147:6; 184:19; 186:1; 212:4; 247:5,  
 10; 249:3; 294:19; 396:12; 422:19  
 recent [8] 5:16; 6:19; 7:2; 190:12; 191:1;  
 192:2; 194:16; 240:19  
 recently [3] 109:7; 250:19; 251:16  
 recessed [1] 197:12  
 recognized [1] 379:13  
 recollection [5] 57:6, 11; 96:6; 100:20;  
 326:14  
 recommend [22] 56:6; 70:3; 75:17; 91:1,  
 15; 100:16; 212:6; 220:8; 221:21; 231:13,  
 19; 268:20; 269:2, 17; 282:14; 294:19;  
 307:9; 360:7, 8; 382:17; 388:20; 413:7  
 recommendation [11] 57:17; 75:11; 84:1;  
 247:8; 355:12; 378:15; 389:7; 398:5;  
 410:18; 413:14, 22  
 recommendations [7] 56:1; 60:1, 9;  
 358:5; 361:1; 403:7; 416:4  
 recommended [13] 74:8; 168:16; 211:13;  
 212:14; 218:10; 220:15; 243:17, 22;  
 244:2; 283:6; 293:3; 322:13; 396:13  
 recommending [4] 246:9; 295:5, 8;  
 404:11  
 reconvene [1] 197:10  
 record [7] 6:14; 8:5; 10:10; 78:6; 130:2, 3;  
 139:21  
 recorded [1] 148:2  
 recur [5] 28:9; 29:6; 187:10; 279:3  
 recurrence [30] 5:7; 6:6; 28:21; 31:18;  
 135:5; 180:21; 181:3, 4; 209:3, 5, 6, 11,  
 14, 17, 18; 235:13; 302:12; 304:12;  
 306:13; 307:17; 315:2; 319:10; 343:3;  
 344:8; 361:14; 362:20; 363:2; 381:19  
 recurrent [3] 7:11; 20:3; 23:15  
 recurring [1] 17:13  
 recurs [2] 30:22  
 recused [1] 8:21  
 red [4] 48:22; 49:16; 147:7; 149:2  
 reduce [6] 114:12; 232:20; 262:6, 17;  
 318:10; 396:15  
 reduced [18] 46:13, 19; 132:19; 133:10,  
 17; 142:19; 148:8; 161:7; 166:8; 182:11;  
 211:19; 222:19; 259:21; 260:9; 266:19;  
 324:12; 334:6; 341:8  
 reduces [2] 12:22; 16:17  
 reduction [12] 38:1; 48:22; 50:13; 133:18;  
 148:11, 16; 149:4; 183:6; 259:19, 20;  
 341:14; 422:12  
 redundant [1] 222:13  
 reemphasize [2] 185:15; 196:13  
 refer [1] 199:7  
 reference [12] 42:11; 62:22; 70:6; 102:18;  
 156:2; 179:19; 188:4; 235:2, 6, 11, 16;  
 272:7  
 referred [4] 27:7; 211:6; 253:14; 264:6  
 referring [5] 212:15; 251:1; 253:12;  
 286:12; 350:7  
 refers [3] 16:3; 422:22; 423:6  
 reflect [6] 112:21; 140:3; 176:11; 291:3,  
 11; 306:8  
 reflected [1] 168:19  
 reflection [2] 168:1; 306:15  
 reflects [4] 154:19; 194:8; 344:17; 345:3  
 regard [27] 8:4; 14:4; 16:21; 17:8; 24:19;  
 25:6, 12; 26:16; 56:5; 90:7; 127:11; 184:5;  
 191:6; 225:5; 292:9; 297:7, 8; 317:21;  
 322:19; 325:3, 14; 331:5; 333:15; 377:14;  
 394:18; 421:4; 422:10  
 Regarding [1] 23:22

regarding [2] 306:20; 339:11  
 regardless [2] 164:16; 292:17  
 regimen [11] 50:2; 210:5, 20; 211:13;  
 230:2; 246:4, 16; 254:13; 358:7; 382:6;  
 421:13  
 regimens [1] 322:12  
 regiment [5] 35:15; 243:18; 260:6, 14;  
 321:16  
 regiments [1] 254:12  
 region [1] 395:19  
 register [1] 112:19  
 registered [1] 301:1  
 registering [1] 233:14  
 regression [1] 250:1  
 regular [2] 136:12; 373:11  
 regulate [1] 408:2  
 regulated [1] 8:10  
 regulatory [1] 324:17  
 reinforced [1] 45:2  
 reiterate [1] 278:6  
 reiteration [1] 188:18  
 rejected [1] 221:9  
 relapse [10] 142:19; 206:5, 8; 304:6, 20;  
 306:11; 307:10, 11; 333:21; 354:8  
 relapsed [3] 208:8, 9; 305:1  
 Relapses [1] 135:5  
 relapses [3] 20:7; 305:14; 306:8  
 relate [4] 50:19; 171:6; 199:21; 310:8  
 related [33] 8:22; 44:16; 62:17, 18; 64:9,  
 16; 99:15; 124:15; 147:21; 152:16; 160:7;  
 164:6, 22; 165:5; 189:14; 198:22; 205:9;  
 210:2; 236:6; 245:5; 252:2; 282:1; 287:7;  
 302:15; 303:1, 3, 10; 306:17; 308:2;  
 311:5; 315:13; 346:22; 380:11  
 relates [5] 16:9; 68:4; 199:1; 242:10;  
 281:22  
 relating [5] 9:3; 68:12; 69:1; 153:9; 168:5  
 relation [4] 179:7; 184:6; 185:5; 186:6  
 relationship [47] 33:2, 7, 9, 21; 35:14;  
 36:5, 11, 16; 49:5, 12, 22; 50:17; 51:3, 19;  
 56:21; 62:7; 66:19; 68:15, 18; 69:4, 13;  
 73:2; 78:16; 84:9; 96:12; 108:19; 110:10,  
 15; 115:19, 20; 116:22; 117:2; 119:5;  
 134:14; 138:13; 142:1; 144:22; 151:17;  
 152:1, 3; 170:22; 177:6, 8; 182:14; 259:3;  
 314:20; 364:9  
 relationships [2] 74:20; 365:8  
 relative [13] 92:11; 125:11; 140:5; 156:10;  
 157:4; 171:12, 15; 178:5; 227:3, 4;  
 289:12; 354:11; 401:14  
 relatively [13] 14:19; 64:11; 101:20; 156:2;  
 186:17; 195:1; 251:13; 316:7; 346:18;  
 348:18; 354:19; 360:2; 362:16  
 relay [1] 301:9  
 release [5] 34:20; 35:4; 89:21, 22; 100:11  
 relevance [1] 320:14  
 relevant [22] 12:1; 30:18; 36:1; 145:18;  
 147:15; 154:3, 11; 161:19, 22; 168:18;  
 169:20, 22; 171:5; 172:6; 173:5; 174:14;  
 212:10; 214:17, 20; 233:20; 290:19; 319:2  
 reliable [1] 121:6  
 reliably [1] 85:10  
 relief [1] 28:17  
 relived [1] 7:13  
 rely [1] 374:21  
 remain [2] 168:4; 205:2  
 remainder [3] 163:9; 184:19; 253:11  
 remained [3] 142:14; 144:4; 179:13  
 remaining [4] 50:21; 69:19; 119:12;  
 203:14  
 remains [2] 19:18; 189:11

- remember [5] 76:17; 98:7; 100:19; 163:9; 323:7  
 remind [4] 175:1; 228:13; 232:19; 403:9  
 reminder [1] 403:15  
 remote [2] 192:3, 8  
 remove [1] 292:1  
 removed [1] 317:16  
 removing [2] 291:19, 20  
 renally [1] 294:13  
 reoccurrence [1] 135:6  
 repeat [3] 61:19; 154:1; 217:17  
 repeated [1] 139:5  
 repeatedly [1] 153:21  
 repetitively [1] 348:17  
 replacement [3] 43:15; 93:15; 94:10  
 replicated [1] 239:21  
 replication [1] 256:4  
 repolarization [3] 6:3; 123:22; 184:10  
 report [3] 77:14; 226:19; 251:2  
 reported [10] 8:8; 9:18, 22; 35:3; 179:18; 185:13; 270:5; 301:12, 13, 21  
 reporting [1] 301:20  
 reports [1] 92:22  
 represent [6] 16:20; 148:11, 13; 157:2; 168:13; 204:7  
 representative [2] 238:22; 272:22  
 representatives [1] 113:11  
 represented [2] 140:13; 172:13  
 represents [11] 42:1, 6; 49:20; 138:8; 143:9, 11; 150:14; 163:4; 185:8; 194:15; 371:6  
 reproduced [1] 238:15  
 reproducible [1] 237:13  
 request [2] 4:16; 368:20  
 requested [2] 4:12; 283:16  
 requests [1] 226:11  
 require [6] 89:8, 9; 116:4; 303:6, 7; 398:11  
 required [5] 70:18, 20; 155:12; 167:3, 6  
 requirements [1] 398:14  
 requires [4] 25:2; 133:4; 307:3; 397:20  
 requiring [4] 14:13; 160:19; 169:19; 359:4  
 Research [7] 4:10; 8:11; 9:8; 11:12, 13; 82:13  
 research [1] 9:3  
 reservations [1] 257:2  
 reserve [1] 388:9  
 residual [1] 45:8  
 resistance [1] 48:17  
 resolution [1] 72:20  
 resolve [1] 391:2  
 respect [4] 9:17; 10:11; 176:11; 399:10  
 respectively [4] 141:5; 162:16; 166:7, 9  
 respond [6] 27:9; 61:7; 224:11; 279:20; 315:22; 391:11  
 responded [1] 421:22  
 response [39] 7:18; 33:2, 8, 13; 50:9, 17; 69:8; 95:19; 131:2; 134:14; 138:12; 141:3, 21; 142:1; 144:21; 151:17; 152:1, 3; 230:9; 238:2; 241:12; 242:17; 259:3; 264:16; 265:1, 20; 266:6; 270:13; 273:16; 279:17; 291:21; 306:5; 307:20; 316:3; 322:14; 333:19; 348:2; 402:16; 406:19  
 responsibility [10] 405:5, 6, 13, 20; 406:4, 9, 10; 408:15, 16  
 responsible [1] 406:2  
 responsive [1] 265:13  
 responsivity [2] 218:15; 279:12  
 rest [9] 67:18; 125:1; 162:22; 214:20; 272:10; 273:6, 7; 354:18; 357:14  
 resting [3] 272:14, 16; 273:15  
 restore [1] 315:14  
 restored [1] 324:19  
 restrict [1] 98:6  
 restricted [2] 202:6; 346:9  
 result [7] 86:15; 134:21; 154:21; 166:19; 178:8; 196:22; 202:20  
 resulted [2] 116:9; 377:5  
 resulting [1] 191:13  
 results [31] 9:13; 11:22; 12:8, 12, 17, 19; 13:3; 18:21; 131:16; 142:13; 144:10; 162:5; 164:21; 165:17; 169:5; 170:5, 13; 171:17; 173:7; 179:8; 192:14; 237:15; 239:21; 242:1; 299:20; 300:16; 318:19; 369:21; 376:17; 377:5; 419:8  
 Retaining [1] 138:8  
 retrieved [1] 322:6  
 retrospective [3] 92:21; 163:15; 256:18  
 return [1] 104:11  
 revealed [1] 157:3  
 reveals [2] 156:14; 164:4  
 reversible [1] 132:7  
 reversion [1] 30:5  
 revert [1] 368:22  
 reverted [1] 278:19  
 reverts [1] 234:13  
 review [10] 4:22; 5:3; 10:17; 31:9; 131:4; 149:19; 194:16; 248:18; 376:15; 417:20  
 reviewed [2] 66:2; 285:17  
 reviewer [1] 421:7  
 reviewers [5] 21:21; 149:16; 198:18; 336:1; 384:17  
 reviewing [1] 130:22  
 reviews [1] 5:2  
 revolves [1] 154:14  
 rhetorical [1] 76:12  
 rhythms [2] 22:21, 22  
 rich [2] 87:6; 185:21  
 rid [1] 368:6  
 Right [27] 54:3; 70:11; 78:21; 80:15; 102:17; 105:21; 106:9; 107:9, 15; 202:10; 211:15; 212:17; 217:3; 218:2; 221:7; 246:17; 269:19; 295:11; 327:18; 344:3; 352:5, 7; 380:2; 386:1; 398:10; 399:8; 415:2  
 right-hand [2] 31:21; 171:7  
 rigid [1] 102:6  
 rigorously [1] 377:17  
 risks [9] 12:5; 13:7; 179:2, 5; 277:16; 388:18; 389:16; 395:17; 396:3  
 Risseau [1] 48:1  
 Rob [8] 4:3; 61:11; 113:7; 255:1; 256:7; 261:22; 311:6; 379:5  
 robust [5] 124:10; 163:4; 284:14; 314:8; 316:21  
 rocket [1] 97:20  
 Roden [1] 8:20  
 role [6] 224:8; 304:11; 408:3, 4, 22; 409:6  
 room [3] 8:18; 10:19; 53:18  
 roughly [6] 32:4, 9; 180:2; 189:2; 194:2; 265:2  
 route [2] 209:15; 355:21  
 routine [3] 133:4; 343:10; 344:12  
 row [1] 83:20  
 ruined [1] 391:20  
 rule [1] 300:14  
 rules [6] 237:9; 342:5; 365:1, 4, 5, 6  
 run [6] 93:10; 99:5; 199:2, 4; 240:12; 270:19  
 running [3] 93:9; 135:22; 199:7  
 runs [3] 6:12; 110:21; 349:11  
 RUSKIN [25] 13:22; 22:14; 23:16; 24:19; 26:5, 10, 15; 27:11; 28:10, 19; 29:8; 30:7; 31:16; 32:4, 14; 178:15; 208:18; 223:19; 280:9; 288:18; 306:6; 308:16; 309:11, 19; 310:15  
 Ruskin [7] 13:13, 21; 170:15, 16; 208:12; 306:3; 308:13  
 RVF [1] 314:21  
 Ryder [4] 11:11; 13:22; 107:18; 342:21

## - S -

- safe [10] 6:7; 24:3, 8; 161:15; 184:14; 196:14; 401:16; 405:2; 412:14, 18  
 safely [2] 62:13; 300:18  
 safer [1] 363:1  
 Safety [1] 288:14  
 sake [1] 59:6  
 salutary [1] 183:15  
 sample [12] 55:7, 12; 110:16; 115:10, 12, 13; 139:3; 204:6; 240:7; 254:14; 316:18; 317:9  
 samples [1] 109:13  
 sampling [1] 109:12  
 SASICH [1] 4:9  
 Sasich [1] 4:9  
 sat [1] 338:2  
 satisfactory [1] 98:1  
 satisfied [1] 349:2  
 save [1] 130:11  
 saying [50] 26:3; 31:17; 54:16; 65:2; 84:22; 91:6; 101:9; 103:21; 110:6; 111:8; 126:9; 128:13; 170:8; 225:5; 231:19; 237:22; 238:1; 240:7; 244:16; 247:17; 255:5; 257:5; 291:4; 292:7; 297:4; 298:16; 302:6; 318:17; 329:18; 331:11; 334:1; 340:12, 13, 19; 343:22; 352:14, 21; 359:18; 360:1; 365:7, 10; 386:2; 392:21; 393:18; 397:16; 401:5; 409:11; 411:12; 416:18  
 scale [2] 26:22; 148:3  
 scanned [1] 192:22  
 scenario [2] 60:2; 234:7  
 scheme [5] 45:20; 46:5; 47:14; 396:13, 15  
 schools [3] 405:15; 406:12; 410:8  
 science [1] 97:20  
 score [4] 147:17, 18; 232:22; 233:6  
 screen [1] 104:18  
 se [1] 347:4  
 sea [1] 107:11  
 seam [2] 92:10; 93:3  
 search [1] 276:7  
 Second [1] 80:3  
 second [22] 55:22; 63:11; 86:7; 120:18; 126:11; 134:21; 143:11; 154:4; 221:18; 238:12; 242:3; 315:12; 332:13; 334:11; 335:5, 16, 22; 336:16; 341:15; 342:19; 345:18; 372:20  
 secondary [6] 16:5; 131:2; 141:10; 145:6; 258:20; 321:13  
 Secondly [1] 97:14  
 secondly [4] 33:19; 200:11; 223:17; 311:13  
 seconds [2] 185:14; 306:18  
 SECRETARY [2] 7:22; 31:22  
 secre... [3] 38:6; 67:3; 90:17  
 secretes [1] 37:8  
 Secretion [1] 35:19  
 secretion [10] 34:9; 35:22; 37:7, 19; 38:8; 39:19, 21; 41:21; 43:12  
 secretary [5] 36:1; 38:5; 54:18; 103:10; 118:11  
 section [2] 158:11; 285:7

sees [1] 368:18  
 segment [2] 263:10; 298:4  
 segmenting [2] 263:11; 264:2  
 segments [1] 66:18  
 segregated [1] 206:13  
 segregation [1] 322:5  
 select [2] 82:14; 191:18  
 selected [1] 379:17  
 self-evident [16] 324:11; 326:16; 327:9;  
 19; 328:7, 11, 12; 329:11; 330:10; 333:22;  
 334:5, 20; 335:11; 339:10; 342:7, 13  
 semantics [1] 117:5  
 send [3] 59:11; 318:8; 343:14  
 sending [1] 407:2  
 Senior [1] 11:11  
 senior [1] 15:11  
 sense [7] 65:6; 131:9; 187:9; 252:19;  
 299:3; 322:11; 410:13  
 sensitive [1] 65:19  
 sensitivity [7] 49:14; 50:1; 57:14; 63:11;  
 79:12; 133:19; 229:4  
 sentiment [1] 108:14  
 separate [4] 73:20; 160:10; 240:5; 264:7  
 separately [1] 375:4  
 sequence [4] 154:1; 243:20; 246:20;  
 293:13  
 series [1] 198:21  
 serious [6] 5:2; 250:16; 373:6; 408:20;  
 412:21  
 seriously [2] 362:17; 417:9  
 serum [11] 46:1; 65:16; 69:18; 77:14, 17,  
 20; 109:12; 132:17; 133:5; 137:2; 397:15  
 serve [2] 33:22; 51:6  
 serves [1] 42:10  
 sessions [1] 255:3  
 sets [2] 181:13; 290:3  
 setting [7] 13:12; 20:20; 149:17; 241:9;  
 350:13; 369:18; 372:6  
 settings [2] 237:12; 239:22  
 seven [2] 102:20, 21  
 Seventy [1] 151:3  
 sever [2] 213:17; 254:15  
 severe [11] 36:13; 159:14; 192:3, 15;  
 193:5; 238:20; 267:10; 293:7; 373:16;  
 394:7  
 Severely [1] 394:1  
 severely [2] 174:3; 393:13  
 severities [1] 149:10  
 severity [5] 145:16; 148:2, 22; 149:3;  
 152:16  
 sex [3] 356:22; 357:1; 358:18  
 SF36 [3] 145:13; 146:15; 147:16  
 shaking [1] 85:13  
 shalt [1] 409:17  
 shape [1] 401:7  
 share [2] 178:18, 22  
 Shaw [3] 417:20; 422:22; 423:6  
 shift [1] 65:18  
 shifted [1] 323:2  
 Shiner [1] 126:22  
 shock [1] 330:1  
 shoed [1] 170:6  
 shoot [1] 361:13  
 shop [1] 413:2  
 shortness [3] 147:22; 148:19; 149:12  
 shot [2] 69:8; 252:12  
 shoulder [1] 94:2  
 showing [11] 15:4; 33:21; 38:20; 103:15;  
 147:12; 188:20; 189:19; 205:4; 226:5;  
 264:16; 320:12  
 shows [24] 36:5; 38:19; 41:14; 46:9, 10;

63:6; 69:13; 70:14; 79:3; 81:4, 11; 94:5;  
 141:16; 148:8; 150:12; 171:15; 193:1;  
 195:8; 205:8; 206:21; 254:20; 264:11;  
 270:22; 344:12  
 sick [6] 25:11; 183:2; 191:10; 194:13;  
 281:4; 293:6  
 sicker [4] 17:22; 188:10; 189:15; 266:21  
 sidetracked [1] 219:15  
 sigh [1] 28:17  
 sigmoid [2] 39:7; 71:13  
 signal [28] 40:4; 42:16; 66:11; 80:13;  
 87:17, 19; 104:14; 109:1; 110:2; 127:4;  
 153:11; 173:19; 187:18; 188:7; 189:9;  
 220:3; 226:16; 237:1; 278:13; 286:11, 16;  
 289:21; 291:5; 292:3, 10; 294:3; 303:17;  
 343:10  
 signals [5] 42:19; 104:17; 116:4; 126:21;  
 287:14  
 significance [9] 21:9; 134:20; 138:14;  
 144:15; 149:9; 150:11; 151:22; 248:13;  
 292:7  
 significant [35] 12:20; 13:6; 17:4; 21:11;  
 25:18; 43:10; 84:16; 86:3; 95:15; 105:12;  
 138:2; 144:19; 150:18; 151:1, 8, 12;  
 156:8, 14; 162:6; 163:6; 164:1; 169:17;  
 181:16; 194:6; 241:16; 244:15; 273:14;  
 277:18; 336:12; 347:15; 388:1; 392:4;  
 393:3, 8, 9  
 significantly [5] 15:13; 95:5; 182:11;  
 388:19; 390:16  
 signs [2] 411:13, 14  
 silent [1] 67:18  
 silly [1] 241:5  
 simple [6] 15:10; 98:13; 267:22; 288:21;  
 374:18; 381:20  
 simpler [1] 261:16  
 simplistic [1] 69:6  
 single [10] 45:12; 49:10; 54:11; 79:7;  
 93:21; 94:6; 185:8; 209:14; 276:8; 341:21  
 sir [1] 305:7  
 sit [3] 10:20; 21:18; 342:22  
 sites [1] 240:8  
 sitting [4] 172:3; 228:19; 343:1; 399:7  
 situation [6] 258:2; 307:1, 6; 387:20, 21,  
 22  
 situations [4] 16:6; 25:17; 29:1; 361:4  
 six [22] 15:2; 31:13; 50:21; 64:2; 139:4;  
 140:18; 147:8, 11; 160:15; 177:20, 21;  
 209:16, 18; 241:4, 19; 248:16; 280:7, 20,  
 21; 290:13; 336:7; 422:15  
 sizable [2] 330:11; 331:13  
 size [7] 55:7, 13; 139:3; 204:6; 316:18;  
 317:9; 351:2  
 sizes [1] 240:7  
 skeptical [1] 330:8  
 slapping [1] 233:17  
 slice [3] 77:1; 285:8  
 Slide [2] 85:19; 270:22  
 slides [10] 10:20; 11:7; 51:5; 102:20;  
 173:22; 175:2; 186:3; 188:17; 213:6;  
 261:4  
 slight [1] 95:12  
 slightest [1] 121:2  
 slightly [6] 190:19; 255:4; 309:15; 318:15;  
 327:1; 357:20  
 slope [15] 36:16, 19; 49:11, 16; 51:3;  
 65:13, 18; 74:19, 20; 75:1; 78:17; 79:6, 7,  
 8; 119:13  
 sloppy [1] 370:10  
 smaller [3] 238:17; 254:14; 407:17  
 smart [1] 98:7

smarter [1] 129:12  
 sneaking [1] 341:20  
 society [1] 405:14  
 sociologic [1] 408:8  
 solely [1] 88:12  
 solution [1] 78:8  
 solve [2] 232:16; 361:20  
 Somebody [1] 418:1  
 somebody [17] 27:13; 31:1; 58:4; 64:5;  
 202:13; 218:2; 228:20; 309:16; 315:11;  
 331:9; 362:21; 366:9; 402:7; 404:14;  
 413:19; 418:5; 422:8  
 Someday [1] 77:18  
 someday [2] 418:5; 420:5  
 somehow [3] 112:2; 254:8; 364:11  
 Someone [2] 81:19; 234:1  
 someone [10] 28:7; 114:12; 231:4, 10;  
 238:21; 267:13; 312:4; 327:17; 346:2;  
 388:17  
 somewhat [12] 17:22; 177:8; 180:6;  
 239:8; 240:22; 280:10; 292:14, 15;  
 309:13; 339:18; 388:13; 390:22  
 somewhere [7] 52:7; 102:21; 122:8, 11,  
 12; 268:4; 362:12  
 sophisticated [1] 305:19  
 sore [1] 106:15  
 sorely [1] 125:9  
 sorry [13] 23:17; 101:6; 128:12; 217:18;  
 229:5; 236:10; 244:6; 269:14; 271:8;  
 272:13; 294:20; 296:10; 344:4  
 sort [45] 104:7; 105:18; 106:1; 110:21;  
 112:17; 114:15; 116:8; 153:9; 177:10;  
 216:20; 237:9, 10, 19; 238:14, 22; 242:19;  
 243:20; 248:12; 252:22; 255:15; 256:7,  
 19; 264:2, 15, 20; 274:6; 275:22; 286:21;  
 288:1; 299:21; 308:2; 311:22; 313:11;  
 321:5; 324:5; 329:17; 355:9; 362:19;  
 363:7; 396:10; 401:6, 17, 18; 405:22;  
 410:9  
 sorted [1] 349:15  
 sorting [2] 37:15; 345:1  
 Sotalol [17] 19:2; 125:16; 135:16; 136:16;  
 180:2; 184:20; 203:17; 205:11; 227:17;  
 271:19; 307:2; 375:7, 8, 11, 15  
 sotalol [1] 227:15  
 sought [1] 417:15  
 source [2] 23:18; 289:14  
 spared [2] 29:7; 330:1  
 sparing [1] 66:22  
 speak [2] 23:4; 207:13  
 speaker [2] 9:18; 153:1  
 speakers [1] 154:13  
 speaking [1] 308:20  
 special [4] 51:14; 122:15; 176:14; 417:14  
 specially [7] 243:14; 286:11; 324:21;  
 334:13, 17; 402:20; 418:10  
 specific [14] 55:1; 60:18; 88:21; 91:16, 17;  
 103:21, 22; 200:15; 211:5; 278:11; 288:7;  
 360:2; 399:18; 416:3  
 Specifically [1] 131:15  
 specifically [17] 44:12; 88:18; 93:13;  
 94:21; 103:12; 179:19; 188:16; 196:8;  
 201:13; 288:9; 289:2; 306:17; 321:2;  
 329:8; 376:20; 404:15; 420:10  
 specified [5] 207:19, 22; 211:3; 271:11,  
 13  
 specify [1] 241:2  
 specifying [1] 353:21  
 spectacular [1] 362:14  
 specter [1] 72:21  
 spectrum [2] 16:21; 153:22

- speculate [1] 224:2  
 Speculation [1] 278:1  
 speculation [3] 224:3; 277:15, 22  
 speculative [1] 224:12  
 spend [7] 110:22; 121:15; 124:7; 185:14;  
 198:13; 201:9; 413:9  
 spending [1] 92:2  
 spent [1] 342:9  
 spermalactone [1] 67:2  
 spirit [3] 264:8; 396:14; 404:22  
 split [1] 205:9  
 spokesman [1] 282:8  
 Sponsor [1] 198:9  
 sponsor [37] 11:8; 13:21; 33:5; 43:19;  
 70:2; 73:19; 84:1; 127:6; 213:16; 225:12,  
 14; 235:20; 238:21, 22; 239:7; 246:3;  
 257:14; 262:11, 21; 288:9; 297:11; 308:8;  
 316:1; 322:13; 326:19; 329:21; 330:8;  
 350:7; 357:14; 376:14; 403:2; 408:11, 15;  
 409:19; 410:4; 417:15, 21  
 sponsors [1] 96:17  
 spreading [1] 300:22  
 squared [2] 36:18; 73:5  
 stability [4] 56:19; 57:2; 63:14; 64:1  
 stable [5] 56:21; 57:10; 63:5, 13; 361:11  
 stakes [1] 52:20  
 STANDAERT [2] 7:22; 31:22  
 standard [2] 312:22; 413:18  
 standing [1] 98:12  
 standpoint [4] 14:15; 202:11, 14; 386:22  
 stands [2] 161:6; 397:9  
 start [36] 4:5; 21:20; 23:20; 47:4; 58:4;  
 63:10; 78:13; 94:15; 100:7, 17; 140:21;  
 175:8, 9; 198:17; 199:22; 212:8; 242:21;  
 244:2; 245:7; 256:17, 20; 278:19; 284:6;  
 292:19, 21; 302:16; 320:3, 18; 347:6;  
 363:11, 13, 17; 364:19; 365:1; 373:1  
 started [17] 130:14; 203:5; 217:1, 21;  
 264:12; 265:21; 270:2, 3; 271:2; 292:17;  
 293:10; 294:6, 22; 295:16; 297:15; 316:2;  
 375:18  
 starting [9] 12:22; 203:15; 247:21; 256:8;  
 259:5, 7; 281:21; 356:18; 365:3  
 starts [2] 216:2; 321:17  
 Stat [1] 185:10  
 stat [7] 193:2, 4, 14, 22; 280:4, 7, 11  
 state [16] 45:14; 46:11; 49:15; 58:19;  
 59:1, 10; 65:15; 94:6, 7; 136:6; 264:21,  
 22; 265:6; 276:11; 308:16; 405:14  
 stated [2] 45:15; 313:21  
 statement [9] 8:1; 10:15; 121:16, 19;  
 223:20; 242:8; 256:1; 261:12; 390:9  
 statements [2] 8:17; 382:17  
 States [3] 14:22; 32:2; 298:19  
 stating [1] 260:4  
 statistic [1] 129:16  
 statistical [13] 134:20; 138:13; 141:3;  
 144:15; 149:9, 19; 150:11; 151:21; 162:3;  
 237:5; 261:8; 284:17; 363:22  
 Statistically [1] 151:11  
 statistically [6] 95:14; 138:2; 144:19;  
 151:1; 164:1; 244:15  
 statistician [3] 207:12; 237:8; 256:16  
 Statisticians [1] 285:5  
 statisticians [2] 263:13; 267:3  
 status [6] 70:10; 146:2; 149:7; 181:22;  
 182:15; 344:18  
 stay [3] 16:6; 203:19; 339:1  
 staying [1] 363:22  
 steady [12] 45:14; 49:15; 58:18; 59:1, 9;  
 65:15; 94:6, 7; 136:6; 264:21, 22; 265:6  
 steepest [1] 82:21  
 steering [3] 293:4, 13; 294:9  
 step [7] 50:2; 92:16; 114:4; 265:19;  
 279:11, 15; 381:6  
 Steve [2] 228:4; 244:1  
 Steven [1] 11:11  
 stick [1] 178:17  
 stimulated [1] 93:13  
 stimulus [1] 403:15  
 stinks [1] 287:11  
 stipulate [1] 383:12  
 stock [1] 10:1  
 stop [18] 28:8, 17, 20; 29:12; 99:7; 100:3,  
 7, 13; 101:7; 178:10; 202:11; 307:11;  
 319:12; 380:6; 395:16; 411:10; 412:14;  
 414:18  
 stopped [3] 201:4; 305:4; 370:3  
 stopping [1] 130:6  
 straight [3] 76:20; 130:5; 309:6  
 strategy [10] 75:22; 265:16; 273:21;  
 274:2; 296:20; 297:2, 5, 7; 299:4  
 stratified [2] 192:2, 15  
 strength [1] 240:17  
 stress [1] 87:8  
 strict [1] 267:2  
 strikes [1] 413:5  
 striking [2] 192:7; 321:14  
 strikingly [1] 310:10  
 stringent [2] 238:18; 391:12  
 strip [1] 84:3  
 stroke [13] 16:13, 17; 250:15, 20; 251:1,  
 10, 16; 267:20; 268:2, 3; 310:21; 325:19;  
 414:8  
 strong [10] 150:11; 187:18; 320:1; 321:7,  
 13; 333:14; 341:19; 344:7; 345:16  
 strongly [7] 135:1; 158:9; 252:6; 335:6;  
 344:19; 350:17; 384:18  
 struck [1] 104:4  
 Structural [1] 350:6  
 structural [37] 12:21; 18:20; 19:4; 20:5,  
 21; 21:16; 137:4; 139:19; 156:11; 157:14;  
 158:1, 12; 163:7; 171:20; 185:19; 194:18;  
 195:11, 19; 196:17; 221:5; 226:12; 267:1,  
 11; 277:17; 287:18, 19; 293:7, 10; 348:7;  
 349:5; 350:13; 351:3, 20; 352:20;  
 353:6; 370:14; 385:9  
 structured [1] 7:5  
 struggle [1] 318:6  
 struggling [2] 292:11; 318:13  
 stuck [2] 283:13; 357:15  
 studied [6] 17:13; 191:5; 309:13; 315:20;  
 349:10; 360:6  
 Studies [1] 135:8  
 Study [5] 47:22; 48:5; 134:17; 135:14;  
 138:15  
 studying [1] 106:19  
 stuff [15] 81:1; 103:22; 106:11; 115:17,  
 19, 20; 232:18; 236:6; 361:8; 365:15;  
 374:21; 395:18; 405:10; 414:18; 416:21  
 stumbling [1] 397:9  
 sub-analysis [1] 163:5  
 sub-investigators [1] 298:9  
 subgroup [1] 192:6  
 subgroups [5] 143:3; 152:12; 157:21, 22;  
 171:8  
 subject [4] 5:20; 293:20; 372:4; 398:20  
 subjecting [1] 390:11  
 subjects [6] 75:7; 165:19; 228:15; 242:19,  
 21; 248:15  
 submission [1] 225:6  
 submit [3] 75:14; 77:5; 258:20  
 submitted [2] 8:7; 17:12  
 suboptimal [1] 337:12  
 subpopulations [2] 131:2; 142:6  
 subselection [2] 317:5, 11  
 Subsequently [2] 37:4; 46:7  
 subsequently [6] 6:17; 36:4; 41:6; 57:10;  
 142:4; 151:6  
 subset [19] 18:14; 26:11; 27:17; 162:12,  
 13; 180:10; 182:9; 191:18; 192:10, 17;  
 308:7; 345:7, 15; 381:15; 383:7; 384:7;  
 386:2, 8, 9  
 subsets [11] 161:19, 22; 162:2; 191:12,  
 13; 195:6; 240:8; 340:20; 382:20; 385:16;  
 390:5  
 subsetted [1] 285:22  
 substantial [9] 39:2; 66:6; 74:11; 100:10;  
 224:6; 237:18; 316:4; 318:11; 321:18  
 substantially [6] 15:15; 65:16; 80:16;  
 317:18; 322:3; 323:4  
 substitute [1] 5:1  
 substrate [5] 80:12; 346:22; 347:3; 370:6,  
 13  
 substrates [10] 38:11, 14; 40:2, 5, 7; 41:4;  
 42:17, 18; 104:22; 105:2  
 substudy [4] 36:14; 46:14; 164:9, 10  
 subtle [2] 18:3; 24:11  
 subtracted [3] 71:15; 177:20; 194:10  
 subtracting [1] 81:5  
 succeeding [1] 299:4  
 success [4] 77:8; 200:9; 202:15; 362:8  
 successfully [3] 135:20; 201:20; 205:2  
 Sudden [1] 165:3  
 sudden [2] 165:5; 387:22  
 sues [1] 405:11  
 suffered [1] 5:18  
 suggest [13] 13:4; 25:20; 61:9; 70:18;  
 100:6; 114:8; 130:4; 149:13; 196:16;  
 197:6; 256:19; 266:9; 387:6  
 suggested [8] 38:16; 105:11; 127:8;  
 250:19; 251:5; 257:5; 361:5; 421:7  
 suggesting [4] 102:2; 254:20; 279:20;  
 305:11  
 suggestion [3] 98:21; 394:15; 403:3  
 suggestions [2] 97:22; 302:10  
 suggestive [1] 351:3  
 suggests [4] 146:19; 265:22; 302:5; 335:7  
 summarize [3] 33:15; 144:10; 151:19  
 summarized [3] 67:20; 282:21; 308:13  
 summarizes [8] 15:19; 18:8; 20:10; 42:21;  
 44:22; 164:12; 179:17; 180:20  
 summarizing [2] 121:17; 417:18  
 summary [7] 121:16; 123:13; 161:2;  
 168:17; 171:4; 195:13; 351:10  
 Superior [1] 143:1  
 superior [3] 152:19; 319:20; 376:9  
 superiority [1] 159:2  
 supraventricular [3] 287:2; 290:6, 8  
 supplement [3] 66:3; 108:17; 174:19  
 supplied [3] 176:13; 272:1; 288:18  
 supply [1] 256:20  
 support [11] 27:14; 121:19; 131:14;  
 230:19; 237:19; 246:15; 326:19; 335:11;  
 338:9; 341:8; 387:7  
 supported [2] 11:18; 235:21  
 supporting [2] 158:6, 9  
 supportive [3] 135:1; 138:17; 144:18  
 supports [1] 38:4  
 suppose [2] 255:5; 369:8  
 supposed [7] 70:12; 111:22; 114:21;  
 204:2; 239:1; 359:18; 365:13  
 suppress [1] 336:20



suppression [6] 5:10; 18:22; 25:17; 190:9; 310:20; 327:9  
 supraventricular [4] 12:19; 21:3; 6; 371:11  
 surgery [3] 317:22; 318:8; 354:2  
 surprise [1] 233:8  
 surprises [1] 366:12  
 surprising [1] 262:5  
 surprisingly [2] 141:2; 240:13  
 Surrogate [1] 338:10  
 surrogate [12] 121:6; 300:16; 305:10, 12; 313:16; 338:4, 8; 340:1; 343:20, 22; 344:1, 2  
 surround [1] 156:18  
 surveillance [1] 404:20  
 survival [11] 153:10; 154:10; 155:3, 16, 22; 156:22; 164:13; 180:14; 187:3; 276:13; 288:4  
 susceptible [1] 214:18  
 suspect [4] 23:7; 67:6; 342:18; 372:16  
 sustained [5] 31:11; 35:4; 89:22; 100:11; 168:8  
 SVA [35] 153:20; 154:3; 155:22; 156:3; 157:3; 158:19; 160:18; 161:1; 164:13; 165:13; 166:10; 167:2, 11; 168:8; 169:9, 13; 171:3; 172:14, 16; 173:9; 175:4; 183:1; 184:7, 17, 21; 186:7; 187:16; 188:19; 216:4, 13; 268:2; 285:18; 287:14, 21; 288:6  
 swamps [1] 15:22  
 switch [1] 305:16  
 Sword [4] 191:4, 16; 291:15, 17  
 sympathetic [1] 242:20  
 symptom [15] 147:18; 148:11, 13, 21; 149:3, 17, 20; 309:16; 325:20; 330:7, 9; 331:7; 333:3; 343:15; 393:8  
 symptomatic [1] 393:19  
 symptomatic [41] 17:14; 19:10; 21:15; 26:1; 131:3; 149:13; 167:6; 179:16; 193:12; 194:18; 195:15; 197:3; 272:11; 273:9, 19; 308:15, 21; 309:6; 336:10; 337:12; 343:5; 346:15, 16; 347:5; 382:19; 386:18, 20, 22; 389:14, 19; 390:10, 16; 391:5, 6, 7, 11, 12; 392:10; 393:12; 394:1  
 syncope [3] 286:17; 287:20  
 syndrome [1] 123:5  
 system [10] 52:13, 18; 54:8; 148:3, 9; 274:21; 281:4; 287:11; 301:20; 405:9  
 systemic [4] 28:11; 36:10; 48:17; 211:4  
 systems [2] 21:12; 77:19  
 systolic [3] 159:7; 161:6; 213:17

- T -

T-max [1] 34:12  
 T-wave [5] 82:17, 18, 19, 21; 83:1  
 table [10] 41:16; 42:5; 78:12; 149:18; 169:18; 207:15; 208:3; 245:22; 346:20; 401:6  
 tables [2] 108:1; 248:11  
 tachyarrhythmias [1] 48:8  
 tachycardia [12] 5:21; 6:13; 122:7, 13; 132:9; 165:10, 12; 166:12; 173:18; 175:17; 236:14; 278:10  
 tachycardias [2] 224:8; 343:14  
 takes [1] 241:10  
 'alk [23] 22:8; 30:3; 84:8; 91:22; 98:21; 123:11; 131:8; 153:1; 186:9; 208:12; 232:11; 235:16; 241:3; 266:16; 281:14; 283:17; 313:14; 329:18; 356:1, 13; 365:13; 398:18; 414:7

talked [5] 270:11; 275:1; 376:15; 383:13; 419:11  
 talking [32] 26:16; 30:8, 9; 31:10; 101:20; 121:16; 128:12, 15, 16; 153:16; 186:10; 228:22; 236:8, 11; 238:7; 260:22; 262:8, 9; 265:18; 304:5; 318:16; 326:8; 334:15; 350:9, 10; 360:17, 19, 20; 363:21; 364:6; 373:1; 399:21  
 talks [1] 198:22  
 Tamoxifen [1] 232:20  
 tangent [2] 82:20, 22  
 tantalizing [1] 319:22  
 taped [1] 232:1  
 target [5] 17:11; 30:2; 132:3, 8; 135:5  
 Targeted [1] 38:17  
 targeted [2] 38:19; 103:12  
 targets [1] 110:6  
 task [2] 349:9; 418:2  
 teacher [1] 77:7  
 team [2] 197:8; 198:9  
 tease [1] 103:12  
 technical [1] 276:6  
 technique [2] 110:18; 272:1  
 techniques [1] 19:15  
 telling [4] 61:13; 97:2; 414:12; 415:3  
 Temple [12] 27:5; 28:20; 130:15; 153:4; 178:16; 215:1; 216:6; 220:10; 259:4; 264:6, 8; 297:21  
 temporal [1] 246:19  
 tempting [1] 421:10  
 ten [19] 83:9, 17, 20; 97:2; 102:21; 106:17; 137:8; 155:4, 10; 166:13; 177:21; 185:14; 216:5; 252:10; 255:6; 265:1; 333:9; 368:16  
 tend [3] 237:12; 277:9; 281:7  
 tended [1] 373:21  
 tendency [1] 87:9  
 tending [1] 265:15  
 tenth [1] 98:9  
 term [14] 25:6, 17; 27:17; 29:21; 117:5; 126:4; 128:1; 131:8, 10; 155:20; 175:6; 334:12, 13; 376:5  
 termed [1] 253:5  
 terminating [3] 6:5; 319:21; 327:13  
 terrible [1] 408:13  
 terribly [3] 14:22; 77:6; 347:19  
 terrific [1] 296:21  
 terrifying [1] 255:19  
 test [14] 103:4; 139:3; 140:17, 20; 141:3; 241:3, 8, 10, 14, 18, 19; 299:20; 376:17; 377:4  
 tested [3] 273:21; 274:2; 346:19  
 testing [1] 242:14  
 tests [2] 241:8, 19  
 textbooks [1] 412:5  
 THADANI [13] 23:22; 26:3, 8; 30:18; 71:22; 98:5; 100:5, 16; 101:3, 7, 12, 17; 102:2  
 Thadani [1] 23:21  
 Thalidomide [1] 300:20  
 Thank [15] 7:14; 10:16; 13:22; 21:17; 32:14, 17; 51:11; 67:16; 70:1; 78:11; 108:12; 152:21; 197:4; 261:22; 423:9  
 thank [8] 11:16; 198:3; 229:11; 251:19; 267:16; 285:4; 376:1; 400:21  
 Thanks [1] 67:22  
 thanks [1] 85:16  
 theme [1] 93:14  
 theoretical [2] 22:15; 339:19  
 Theoretically [1] 38:6  
 theoretically [2] 387:10, 11

therapeutic [19] 12:10; 13:10; 14:18; 19:5; 21:14; 53:14; 68:4, 7, 8, 11; 71:5; 72:22; 178:21; 179:7; 194:19; 195:1, 18; 265:9; 266:10  
 therapeutics [2] 194:16; 406:15  
 therapies [1] 19:7  
 therapy [28] 14:13; 16:16; 17:2; 19:17, 18; 25:2; 26:2; 31:2; 43:15; 56:22; 58:13; 64:2; 74:8; 93:15; 94:10; 109:11; 132:18; 136:4; 174:8; 209:12; 262:19; 264:12; 265:21; 308:22; 310:21; 330:20; 378:7, 14  
 thereby [2] 36:2, 21  
 therein [2] 34:18; 36:3  
 they've [6] 121:10; 233:16; 281:6, 16; 311:14; 406:22  
 thiazide [4] 67:6; 112:5, 7, 9  
 Thiazides [2] 109:4; 110:4  
 thiazides [4] 66:8; 112:14; 113:20; 118:21  
 thinking [18] 51:7; 195:7; 209:8; 223:13; 229:1; 232:11; 243:8; 246:1; 252:11; 292:15; 297:3; 317:21; 378:5; 386:16; 395:20; 407:13; 421:6, 10  
 third [2] 296:14; 329:22  
 thirds [2] 95:17; 294:18  
 Thirteen [1] 263:11  
 thirteen [2] 144:4; 263:18  
 thoroughly [1] 398:2  
 thou [5] 231:11, 14; 409:17  
 thoughts [5] 27:16; 51:7; 178:18; 297:11; 338:7  
 thousand [2] 153:20; 284:12  
 thousands [1] 15:20  
 threatening [3] 7:4, 10; 338:12  
 Three [1] 13:14  
 threshold [1] 218:22  
 thromboembolic [1] 31:7  
 thrombolytic [3] 316:15; 317:17; 318:21  
 throw [1] 255:9  
 thumb [1] 106:15  
 TIA [1] 268:4  
 tight [1] 403:6  
 tightly [2] 65:3; 102:6  
 Tikosyn [6] 8:22; 9:3, 10; 10:4; 11:17; 12:1  
 Till [1] 263:12  
 Tilman [1] 13:17  
 times [13] 48:11; 85:7; 100:21; 109:12; 110:17; 140:12; 174:21; 245:10; 275:18; 289:19; 336:4; 344:1  
 titled [1] 62:6  
 titrated [1] 70:13  
 titrating [1] 229:21  
 titration [2] 230:3; 361:8  
 tolerable [1] 361:12  
 tolerance [3] 18:3; 27:19; 310:8  
 tolerated [6] 183:21; 196:5; 265:16; 376:3, 4; 379:3  
 Toltizim [1] 420:11  
 Tom [34] 223:11; 272:21; 277:6; 281:17; 283:20; 320:17; 321:8; 331:16; 334:14; 337:2; 341:1; 346:6; 350:4, 21; 357:22; 372:5, 12; 374:3; 377:9; 378:3; 383:1, 20; 389:11; 390:14; 391:17; 392:15; 394:18; 399:2; 402:13, 15; 408:6; 415:17, 20; 419:3  
 topic [2] 153:6; 165:3  
 Torsades [1] 366:7  
 tossed [1] 386:18  
 Total [1] 205:13  
 total [29] 20:10; 38:22; 42:7, 8; 50:11; 74:4; 95:3; 96:9; 109:12; 135:11; 156:2;

160:13, 15; 161:17; 163:16; 167:11;  
169:21; 170:6; 173:12; 177:14; 206:12;  
208:2; 210:12; 216:11; 251:22; 255:6;  
285:20; 286:17; 353:1  
totally [4] 107:11; 236:17; 241:2; 242:9  
touch [1] 113:15  
tough [2] 287:13; 314:13  
towards [4] 17:4; 118:17; 319:9; 334:10  
toxic [1] 128:9  
toxicity [7] 24:7; 25:7; 68:9; 98:14; 264:7;  
334:14; 378:11  
tradeoff [1] 319:7  
traditional [3] 37:17; 275:10; 314:18  
tragic [1] 7:12  
trail [1] 203:20  
training [1] 351:17  
translate [1] 44:20  
translates [2] 153:11; 282:9  
transport [6] 18:12, 15; 25:19; 39:7;  
108:22; 195:17  
transported [1] 39:8  
trap [1] 393:4  
treat [15] 4:19; 14:16; 15:15; 25:13; 26:17;  
138:4, 22; 156:4; 158:22; 161:12; 163:18;  
209:19; 213:17; 214:1; 390:5  
treated [20] 26:1, 7; 140:1; 144:8; 149:14;  
158:19; 176:1; 181:15; 182:12; 196:18;  
202:16; 212:13; 249:16; 296:11; 297:13;  
308:11; 318:18; 353:21; 354:3; 369:20  
treating [7] 13:10; 16:8; 98:18; 154:12;  
178:22; 224:19; 345:19  
treatments [1] 318:3  
tremendous [1] 374:6  
tremendously [1] 371:22  
trend [9] 7:1; 140:15; 141:3; 148:16;  
149:3, 6; 190:6, 19; 241:18  
trends [2] 147:11; 148:21  
Triamterene [1] 90:17  
triamterene [2] 67:1, 2  
triggered [2] 59:18; 92:3  
triggers [2] 124:16; 224:9  
Trimethoprim [1] 90:18  
trivariate [1] 364:6  
trivial [2] 77:12; 323:8  
trouble [5] 99:6; 124:13; 125:5; 409:12;  
413:3  
troubled [1] 6:15  
troubles [1] 262:14  
troublesome [2] 27:9; 310:7  
true [26] 23:7; 81:15; 111:17, 22; 113:6;  
123:2; 217:22; 223:16, 17, 18; 255:11;  
257:18; 269:8; 278:5; 280:9; 296:15;  
301:19; 302:6; 344:17; 346:8; 348:19;  
353:8; 361:10; 378:8; 386:5; 395:15  
truly [2] 339:7; 363:20  
trust [3] 387:15; 396:22; 415:22  
tubal [1] 66:19  
turning [2] 155:22; 387:22  
turns [1] 331:21  
twelve [4] 135:14; 147:11; 263:19; 336:7  
twice [9] 46:18; 47:5; 210:15; 229:5, 7, 9,  
10; 234:14; 259:21  
two-fold [1] 311:16  
two-thirds [1] 94:1  
type [15] 44:5; 117:16; 145:4; 186:17;  
209:6; 250:16; 251:6; 258:6; 264:16;  
277:16, 19; 278:5; 308:10, 11; 378:12  
typical [4] 114:7; 117:22; 137:14; 273:1  
typically [2] 212:2; 293:14

## - U -

U.S. [5] 11:12; 15:6; 48:6; 92:17; 281:7  
Udho [2] 26:13; 30:17  
ultimate [2] 78:7; 202:15  
ultimately [5] 160:20; 200:7; 201:20;  
203:7; 272:7  
ultraconservative [1] 53:4  
umbrella [1] 350:10  
unadjusted [3] 143:15; 157:4; 284:10  
unanimous [3] 344:7; 348:4; 354:12  
unanimously [1] 354:7  
unaware [1] 16:22  
uncomfortable [2] 61:3; 418:9  
uncommon [2] 12:6; 15:1  
underestimate [2] 399:3, 4  
undergo [1] 202:19  
underlying [2] 143:17; 347:6  
understand [22] 33:2, 7, 10; 105:14;  
231:5; 237:21; 247:14; 257:2; 266:8;  
267:16; 312:15, 16; 316:19; 351:18;  
357:1; 365:17; 397:2; 398:5; 400:2;  
406:18; 409:14; 412:9  
understanding [2] 66:9; 155:15  
understands [2] 324:15; 398:1  
understood [3] 14:14; 252:5; 396:1  
undertake [1] 397:21  
underwent [1] 136:9  
underwhelmed [3] 325:13; 326:1, 5  
unequivocal [1] 134:18  
unexpectedly [1] 104:7  
Unfortunately [2] 25:10, 216:20  
unfortunately [3] 14:14; 16:15; 210:6  
uniformly [1] 340:12  
unimportant [1] 354:19  
unique [6] 162:20; 281:3, 12; 307:1, 6;  
312:14  
unit [2] 98:12; 411:22  
United [3] 14:22; 32:2; 298:19  
univariate [1] 171:4  
univariant [2] 167:17; 185:16  
universe [2] 86:22; 255:22  
University [1] 32:21  
unknown [4] 35:5; 107:11; 412:19  
unknowns [1] 395:18  
unlike [1] 115:6  
unlikely [1] 39:7  
unmasked [1] 6:3  
unmasking [1] 192:9  
unprecedented [1] 74:16  
unreasonable [1] 264:19  
Unstable [1] 251:11  
unstable [2] 132:6, 7  
unusual [3] 73:13; 90:8; 291:21  
Upjohn [2] 10:1, 3  
upper [2] 47:8; 128:7  
upward [1] 230:3  
upwards [2] 148:12; 229:22  
urge [4] 7:8; 29:4; 67:9; 422:2  
urging [1] 409:19  
usage [1] 406:16  
useful [5] 87:2; 197:1; 276:20; 289:7;  
306:1  
user [1] 408:12  
users [1] 76:14  
usual [1] 65:20  
utility [2] 13:11; 279:8  
utilization [1] 23:11  
utterly [1] 397:17

## - V -

valiant [1] 198:4  
valid [2] 280:8; 291:12  
validated [1] 145:12  
value [21] 36:18; 38:22; 42:10; 44:21;  
79:7; 125:5; 140:19; 141:1, 4, 9, 19;  
151:1, 12; 219:2; 239:17; 240:14; 241:13;  
252:11; 255:11; 256:22  
values [15] 45:9; 46:22; 47:9; 69:18;  
77:17; 105:3; 125:3; 144:20; 147:4, 18;  
239:16; 240:14, 21; 256:17; 336:3  
valve [2] 24:3; 352:10  
vantage [2] 106:1; 121:17  
variability [12] 33:19, 20; 36:20; 45:4, 9,  
15; 46:7, 8; 50:3; 68:2; 73:22; 261:9  
variable [1] 125:2  
variables [1] 33:10  
variate [1] 363:20  
variation [1] 93:14  
variety [4] 40:21; 41:5; 179:18; 255:6  
vary [1] 124:3  
varying [2] 97:1; 402:22  
vascular [2] 48:17; 251:13  
vast [3] 20:12; 21:2; 301:12  
vastness [1] 138:3  
vein [1] 237:7  
veins [1] 224:9  
ventricular [26] 5:21; 6:10, 12; 47:21;  
48:7, 8, 15; 122:7, 12; 132:9; 165:10, 12;  
166:12; 168:12; 173:18; 175:16; 191:2;  
192:8; 193:6; 270:13; 273:16; 278:10;  
315:15; 338:12; 349:4; 389:22  
venue [1] 359:5  
Verapamil [24] 34:20; 35:3, 5; 39:9; 43:13;  
89:1, 11; 99:2, 3, 7, 21, 22; 100:3, 11, 20;  
101:4; 102:12; 103:3, 8; 104:5; 108:2;  
177:14; 178:6; 360:3  
verapamil [1] 95:10  
verify [1] 231:5  
version [3] 12:15; 215:16; 394:22  
versions [1] 169:10  
versus [25] 22:10; 23:14; 69:8; 73:21;  
78:18; 103:18; 181:2, 6, 14, 15, 18;  
188:21; 189:5; 192:3; 193:7; 204:21;  
209:12; 244:13; 247:21; 287:15; 290:17;  
364:4; 376:19; 401:15  
vertical [2] 50:22; 216:4  
VF [1] 168:8  
via [5] 37:9, 16; 38:4; 41:20, 42:3  
vial [2] 407:16  
Vice [1] 11:11  
vicinity [1] 52:8  
victory [1] 273:12  
view [6] 97:12; 121:1; 126:6; 232:14;  
345:4; 384:13  
viewed [1] 273:11  
views [2] 299:5; 391:10  
Virtually [1] 246:20  
virtually [5] 28:15; 185:17; 193:15; 194:13,  
19  
vis [2] 52:6  
visit [7] 108:22; 139:6; 269:4; 343:10;  
344:12; 373:12; 410:5  
visits [1] 136:13  
visualize [1] 264:20  
vitro [4] 40:21; 43:3; 94:12, 19  
vivo [1] 40:22  
volume [2] 45:7; 95:12  
volunteers [5] 5:12, 19; 44:11; 62:7;  
229:10  
vote [12] 322:8; 344:4; 351:15; 356:6;  
382:9, 11; 383:4; 384:4, 8; 385:8; 386:11;

387:13  
 voted [5] 384:7; 385:15, 19; 386:2; 387:1  
 voting [1] 383:5  
 VT [1] 168:8  
 vulnerability [1] 314:16  
 vulnerable [1] 370:12

---

- W -

---

Wait [1] 415:6  
 wait [4] 61:12, 15, 18; 361:13  
 waiting [1] 228:20  
 waiver [1] 8:17  
 waivers [1] 8:15  
 walk [1] 273:18  
 walking [1] 273:8  
 wall [2] 34:8; 158:14  
 wandered [1] 250:17  
 wanted [14] 71:12; 100:2; 114:11; 208:18;  
 227:9; 246:19; 247:11; 251:20; 257:13;  
 277:3, 15; 356:13; 376:14; 388:4  
 wants [4] 107:18; 157:21; 198:9; 391:11  
 war [1] 226:21  
 wards [1] 298:8  
 Warfarin [1] 310:18  
 warned [1] 224:16  
 warrant [5] 39:12, 22; 110:5; 401:19;  
 402:1  
 warrants [1] 390:19  
 wash [1] 288:3  
 Washington [1] 4:10  
 waste [1] 344:20  
 watch [1] 99:8  
 wavelength [1] 22:20  
 wax [1] 36:9  
 ways [12] 53:1; 76:22; 110:21; 111:18;  
 94:8; 240:5; 252:20; 285:8; 305:20;  
 361:20; 396:21; 420:21  
 We've [4] 80:9; 262:4; 286:17; 327:3  
 we've [37] 68:5; 69:17; 76:19; 125:13;  
 130:12; 160:22; 165:4; 171:5, 15; 198:11;  
 214:8; 215:2; 222:14; 226:10; 250:17;  
 261:21; 262:1, 8, 9; 296:22; 315:16;  
 319:19; 324:5; 333:13, 15; 345:12;  
 348:11; 353:16; 365:10; 381:11; 386:17;  
 388:10;  
 391:10; 393:2; 404:1, 3; 420:10  
 weak [1] 325:11  
 weakness [1] 18:2  
 website [1] 233:4  
 wed [1] 61:10  
 Wee [1] 214:17  
 week [4] 135:13; 148:4; 207:22; 366:4  
 weekly [1] 413:2  
 weeks [1] 102:13  
 weigh [5] 239:15; 319:15; 347:13; 354:14;  
 374:13  
 weight [7] 44:15; 45:8; 77:20; 133:6;  
 356:22; 357:1; 358:16  
 weights [1] 357:6  
 weird [1] 327:1  
 well-defined [1] 17:20  
 Weren't [2] 128:13, 17  
 weren't [10] 85:14; 111:21; 176:13;  
 263:21; 293:18; 308:15; 336:1; 343:12;  
 379:14; 387:3  
 whatsoever [2] 121:19; 297:22  
 whenever [2] 191:9; 269:4  
 Whereas [1] 247:8  
 whereas [4] 118:1; 146:12; 148:12; 209:5  
 wherein [1] 138:4

Whereupon [3] 130:1; 197:11; 423:10  
 whichever [1] 218:19  
 white [2] 49:19; 229:6  
 wide [5] 153:22; 156:17; 158:3; 169:7;  
 186:15  
 widely [7] 16:14; 18:19; 19:3; 20:16, 19;  
 193:11; 300:22  
 width [1] 53:14  
 willing [1] 237:10  
 willing [6] 235:19; 243:19; 274:4; 300:9;  
 331:11; 389:14  
 wind [1] 217:16  
 winded [1] 385:8  
 window [1] 207:22  
 wisdom [1] 28:19  
 wise [1] 381:7  
 wish [5] 10:14; 15:9; 307:16; 380:12;  
 381:21  
 withdrawal [1] 183:14  
 withdrawn [2] 6:17; 268:10  
 witnesses [1] 356:10  
 women [12] 32:3, 5, 8; 44:21; 78:18; 79:9;  
 92:17, 22; 96:4; 220:5; 358:20; 359:13  
 won't [5] 159:12; 186:8; 202:11; 303:21;  
 407:20  
 wonder [10] 68:10; 73:19; 76:5; 85:16;  
 126:20; 262:21; 282:17; 304:9; 311:7;  
 391:10  
 wondered [4] 55:6; 56:5; 66:17; 281:19  
 wonderful [1] 313:6  
 wondering [2] 23:12; 294:2  
 Woodcock [1] 255:21  
 word [7] 115:6, 7; 235:4; 325:17; 343:22;  
 370:8, 9  
 wording [1] 394:18  
 words [11] 14:7, 9; 83:7; 205:22; 259:2;  
 265:14; 325:16; 390:17; 393:17; 416:1, 6  
 work [31] 22:15; 23:5; 31:3; 78:1, 14;  
 83:6; 98:13; 111:18; 223:9, 15, 21;  
 224:17; 225:7, 8; 230:14; 235:12, 21;  
 236:3, 5; 254:6; 255:8; 274:20; 299:13;  
 300:7; 316:8; 347:11; 351:16; 360:4;  
 363:17; 382:8; 401:20  
 worked [1] 254:13  
 working [6] 113:20; 223:14; 283:8; 303:1;  
 304:8; 365:22  
 works [17] 47:14; 132:22; 225:18; 231:2,  
 5; 242:12, 13; 245:13; 254:14; 255:10;  
 274:18; 303:1; 355:10; 361:9; 365:15, 17  
 world [14] 175:19; 176:11; 187:14, 15;  
 208:11; 315:10; 344:18; 366:20; 367:18;  
 369:5; 370:3; 372:6; 373:22; 419:16  
 worried [11] 59:19; 99:8; 104:9; 105:19;  
 233:17; 281:8; 283:19; 330:10; 346:9;  
 385:19, 20  
 worry [11] 52:15; 90:4; 101:10; 147:21;  
 148:15, 19; 250:5; 276:15, 17; 277:4;  
 289:20  
 worrying [3] 201:10; 242:21; 342:9  
 worse [5] 54:10, 21; 159:14; 371:19;  
 379:7  
 worsening [3] 149:21; 181:10; 182:10  
 worst [1] 106:13  
 worth [9] 92:1; 121:18; 234:2; 394:2;  
 401:12; 407:4, 14; 414:12; 415:3  
 worthwhile [2] 299:17; 337:19  
 wouldn't [15] 52:13; 64:22; 67:5; 94:11;  
 107:12; 117:4; 231:13; 263:14; 355:19;  
 369:13; 383:8; 407:22; 413:8; 416:3, 20  
 Wow [1] 308:14  
 wreak [1] 369:12

write [3] 115:11; 412:5; 414:5  
 writing [2] 231:11; 243:3  
 written [5] 20:11, 12; 21:2, 6; 287:12  
 wrong [4] 63:2; 294:21; 365:14; 422:8  
 wrote [3] 255:4; 341:5; 376:19

---

- Y -

---

Ye [1] 150:14  
 year [27] 15:20; 16:1; 156:6; 159:18;  
 163:2, 19; 164:16; 179:14; 180:2, 8;  
 187:15; 189:1; 200:12; 209:4, 12; 223:6;  
 259:1; 268:21; 269:2; 275:3, 9; 304:6;  
 306:12, 14; 370:22; 407:7  
 years [12] 123:7; 135:13; 169:15; 172:8;  
 175:22; 213:19; 275:5; 313:22; 314:19;  
 338:3; 369:1  
 yellow [2] 205:13; 206:12  
 yielding [3] 181:4, 18; 182:12  
 You've [6] 73:2; 156:13; 169:10; 180:14;  
 181:7; 183:20  
 you've [28] 26:21; 52:3; 73:20; 95:10;  
 102:13; 154:4; 159:13; 173:21; 174:1;  
 177:7; 179:8; 180:1, 9; 184:3, 11; 188:19;  
 193:7, 21; 209:6; 277:7; 285:17; 289:19;  
 296:18, 20; 305:13; 339:11, 15; 409:3  
 young [5] 44:11; 62:7; 79:8, 9  
 younger [1] 15:1  
 yours [1] 120:14  
 yourself [4] 4:8; 89:16; 273:17; 313:21

---

- Z -

---

zero [7] 72:6; 138:6; 140:12; 227:16;  
 228:15; 326:11; 371:18  
 zone [1] 247:11