FOOD AND DRUG ADMINISTRATION

+ + + +

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + + +

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING

+ + + + +

WEDNESDAY, DECEMBER 12, 2007

+ + + + +

The Committee convened at 8:00 a.m. in the Chesapeake Ballroom of the Sheraton

College Park, 4095 Powder Mill Road, Beltsville, Maryland, William R. Hiatt, M.D., Chair, presiding.

COMMITTEE MEMBERS PRESENT:

WILLIAM R. HIATT, M.D., Chair
ROBERT A. HARRINGTON, M.D.

FREDERICK J. KASKEL, M.D., Ph.D.
ABRAHAM MICHAEL LINCOFF, M.D., F.A.C.C.

TEMPORARY MEMBERS PRESENT:

RICHARD CANNON, M.D.
BARRY M. MASSIE, M.D.

THOMAS SIMON

DESIGNATED FEDERAL OFFICIAL PRESENT:
LCDR CATHY A. MILLER, M.P.H., R.N.

FDA PARTICIPANTS PRESENT:

THOMAS MARCINIAK, M.D.
NORMAN STOCKBRIDGE, M.D.

TABLE OF CONTENTS

P R O C E E D I N G S

8:04 a.m.

CHAIR HIATT: I'm William Hiatt from the University of Colorado and I specialize in vascular medicine. I'm the current chair of the Committee. I want to welcome all of you today.

I guess I'd like to go around the room and have everyone introduce themselves.

Dr. Harrington, can you start?

DR. HARRINGTON: Bob Harrington, I'm an interventional cardiologist at Duke and the director of the Duke Clinical Research Institute.

DR. MASSIE: I'm Barry Massie, Professor of Medicine at the University of California in San Francisco and Chief of Cardiology at the San Francisco VA and I'm a general cardiologist with research interest in heart failure.

DR. LINCOFF: I'm Lincoff, an interventional cardiologist at the Cleveland

Clinic. I am director of cardiovascular research.

LCDR MILLER: Cathy Miller with the FDA.

MR. SIMON: Tom Simon from Atlanta, Georgia. I am the patient advocate for the Committee. I also have atrial fibrillation. I've had it for about 12 years.

DR. CANNON: I'm Richard Cannon. I'm clinical director for the Division of Intramural Research for the National Heart, Lung, and Blood Institute. And I'm head of clinical cardiology at the Clinical Center in Bethesda.

DR. KASKEL: Rick Kaskel, Chief of Pediatric Nephrology at Albert Einstein in the Bronx.

DR. STOCKBRIDGE: I'm Norman Stockbridge. I am the director of the Division of Cardiovascular and Renal Products at FDA.

CHAIR HIATT: All right, as we

begin, I have to read this opening statement for you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the chair.

In the spirit of the Federal Advisory Committee Act and the government and the Sunshine Act, we ask that the Advisory Committee members take care that any conversations about today's topic take place in the open forum of the meeting and not during breaks or lunch.

We are also aware that members of the media are anxious to speak with FDA about these proceedings. However, like the Advisory

Committee members, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

And finally, I'd like to remind everyone present to please silence your cell phones and pagers if you've not already done so. We look forward to an interesting and productive meeting. Thank you for your participation.

LCDR MILLER: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and consultants are special government employees or regular federal employees from other agencies and are subject to federal conflict-of-interest laws and regulations.

The following information on the status of the Committee's compliance with federal ethics and conflict-of-interest laws

covered by, but not limited to, those found at 18 U.S.C. 208 and 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Committee are in compliance with federal ethics and conflict-of-interest laws. Under 18 USC 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of

today's meeting, members and consultants of this Committee who are special government employees have been screened for potential financial conflict of interests of their own as well as those imputed to them including those of their spouses or minor children and for the purposes of 18 USC 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application 22123 Pulzium, tedisamil sesquifumarate, IV solution, two milligrams per milliliter for the proposed indication of use for conversion of atrial fibrillation or atrial flutter to normal sinus rhythm. Based on the agenda for today's meeting and all financial interests reported by the Committee members and consultants, financial conflict-of-interest waivers have

been issued in accordance with 18 USC 208(b)(3) and 712 of the FD&C Act for Dr. Barry Massie. Dr. Massie has been granted these waivers for being a member of a steering committee on an unrelated issue for an affected firm. Dr. Massie receives less than $10,001 per year. The waivers allow this individual to participate fully in today's deliberations. FDA's reason for issuing the waiver are described in the waiver document which are posted on the FDA website. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 630 of the Parklawn Building. A copy of the statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

We would like to remind members and consultants that if the discussion involves any other products or firms not

already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationship that they may have with any firms at issue.

Thank you.

CHAIR HIATT: Thank you. Dr. Stockbridge?

DR. STOCKBRIDGE: Good morning. Once again, I want to thank the Advisory Committee members and temporary voting members on the Committee today. I also want to -- we usually recognize when one of our family leaves to go elsewhere and I wanted to note that this is probably the last meeting for Lieutenant Commander Miller. I want to thank you for all that you've done for the last I think it's last three years you've been here?

Great. Thank you very much.

(Applause.)

The topic today should be fairly familiar. The questions will sound quite familiar. Let's see if the discussion and the answers seem to be similar to what we heard yesterday.

CHAIR HIATT: I think we can proceed to the sponsor's presentation.

DR. RACZKOWSKI: Good morning, Mr. Chairman, members of the Advisory Committee, FDA representatives, ladies and gentlemen.

Today, we will be presenting an overview of tedisamil, a Class III anti-arrhythmic agent.

My name is Victor Raczkowski and I'm the vice president for U.S. Regulatory Affairs at Solvay Pharmaceuticals.

We propose that tedisamil be indicated for the rapid conversion of atrial fibrillation or flutter to normal sinus rhythm. And during our presentations today,

we hope to make several key points: that the conversion to normal sinus rhythm is both rapid and sustained. Conversion typically occurs within 30 minutes and once patients have converted the rhythm is maintained in normal sinus rhythm for at least 24 hours in most cases.

We believe that men and women should receive different doses of tedisamil and that we have performed a robust evaluation of the pro-arrhythmic potential of tedisamil through Holter monitoring.

We believe that tedisamil has a favorable overall benefit-to-risk balance, but in addition, there has a favorable benefit-to-risk balance in key subgroups including in the elderly and patients with mild to moderate renal impairment, patients receiving beta blockers, with Class I-II congestive heart failure and with arrhythmias of longer duration. And importantly, Solvay is committed to the implementation of a risk

minimization action plan and to the performance of observational studies to enhance the safe use of tedisamil in clinical practice.

Joining me at the podium today will be Dr. Peter Kowey. Dr. Kowey will describe the medical need for additional pharmacological agents in this area of therapy.

In addition, we have Dr. Matthias Straub, who will be describing the efficacy and safety data that we are presenting in our application.

Dr. Sands will be providing an overview of our post-marketing plan, and then Dr. Kowey will return to the podium to describe the overall benefit-risk profile of tedisamil. And then we'll be happy to take questions from the Committee.

To help answer your questions we have invited two cardiovascular arrhythmia specialists today. I've already mentioned Dr.

Kowey. Dr. Kowey is the William Wikoff Smith Chair in cardiovascular research and Professor of Medicine in Clinical Pharmacology at Jefferson Medical College.

In addition, Dr. Albert Waldo is the Walter H. Pritchard Professor of Cardiology, Professor of Medicine and Biomedical Engineering at Case Western Reserve University.

Tedisamil has been shown in animal studies to be a Class III anti-arrhythmic drug. It blocks multiple cardiac potassium currents including IKr and two atrial-specific currents, the ultra rapid potassium current, as well as IK-acetylcholine.

Consequently, it prolongs both the action potential duration and the cardiac refractory period. It decreases heart rate and increases blood pressure. And notably in dog models, it converts both atrial fibrillation and atrial flutter to normal sinus rhythm.

In our early clinical development program we identified a two-step infusion regimen in which men and women received different doses of tedisamil. This regimen was based on pharmacokinetic modeling and involves an initial 10-minute infusion in which the first half of the dose is administered and then a second half of the infusion in which the second half of the dose is administered.

Through feedback we've received from the FDA during the review, we are proposing that this infusion be done with two separate bags. FDA has not yet had an opportunity to review this proposal, but it may be a topic of discussion that will be further clarified by Dr. Sands.

We have performed five Phase III studies and there were separate studies in men and women. As discussed and agreed to with the Agency, the primary endpoint was conversion to normal sinus rhythm. We

performed Holter monitoring to evaluate efficacy, the conversion to normal sinus rhythm, as well as to evaluate safety.

We performed four-week safety monitoring. Notably the designs of our Phase III studies were of similar design and that allowed us to pull the data from these studies and then to evaluate questions of interest and the effects of tedisamil in subpopulations of interest.

Notably, all five studies were positive on the primary endpoint.

In our safety database, over 1,100 patients have been exposed to intravenous tedisamil. Of these, 931 subjects had atrial fibrillation and/or flutter. We used intensified monitoring to detect these arrhythmias. These are arrhythmias reported not only by the investigators as adverse events, but in addition those that may have not been reported by the investigators or detected by the investigators were identified

by Holter monitoring.

These Holters were independently reviewed by an Adjudication and Oversight Committee and were centrally analyzed.

We recommend that tedisamil be used in an appropriate clinical setting with continuous electrocardiographic monitoring and with personnel who are knowledgeable and experienced in the use of cardiac arrhythmia agents. Careful patient selection is an important component and we believe that only patients with recent onset atrial fibrillation/flutter should receive tedisamil.

We've also, as I've indicated, proposed gender-specific dosing and administration and the duration of monitoring is for two hours after the start of infusion and when the QTc interval returns to normal.

So in conclusion, we hope that you will have the opportunity to review our data and again, to emphasize the main points that we like to make, we believe that tedisamil has

both rapid and sustained conversion to normal sinus rhythm and that it's effective and safe in the various subgroups that have indicated before. It has an overall favorable benefit-to-risk balance and its safe use in clinical practice will be enhanced both by the risk minimization action plan and observational studies.

It is now my pleasure to introduce Dr. Peter Kowey who will describe the medical need for additional pharmacological agents in this area.

Thank you.

DR. KOWEY: Dr. Hiatt, and members of the Advisory Committee, I feel like it's a little bit like Groundhog Day. We're going to have a chance to relive the experience of yesterday to some extent, although what I'll do in my presentation is if Dr. Pritchett yesterday said he'd be brief, I promise you I'll be very brief, but what I want to do today is emphasize a few key points from

9794f29f-afdd-43a9-98b8-c39d54484326

yesterday's unmet need presentation that Dr. Pritchett gave. And perhaps amplify a few points that are more germane to the application that you're going to see today so we can place it in some perspective.

As you heard yesterday, we are facing an epidemic of atrial fibrillation, not only now but in the several years to come mainly because of the aging of the population, but also because we're managing to keep people alive a lot longer with diseases that used to be fatal and because people are around with things like heart failure and ischemic heart disease and valvular disease, they face the prospect of developing atrial fibrillation. So we expect that this disease not only will have an impact in the next few years, but in decades to come.

It is associated with substantial morbidity and there is a mortal risk associated with atrial fibrillation. That was described very well yesterday. Obviously, our

principal concern is the development of cerebrovascular accidents and stroke, but also heart failure which is a concomitant of atrial fibrillation.

And it has a significant economic impact, not only because of the high density of physician visits that are mandated when patients with this disease are managed appropriately, but also because they find themselves in the hospital very frequently, and hospitalizations with atrial fibrillation are not trivial. They frequently last at least two to three days and commonly cost in excess of $5,000 to $7,000.

As you'll hear today and this is one of the points that I'll spend a little bit of time differentiating, as you'll hear today, there's been a strong emphasis in this application on study of the efficacy and safety of this drug in women. Women live longer lives and consequently the prevalence of disease in the elderly women in this

country is higher than in men. Women tend to have worse cardiac outcomes and that is also true with atrial fibrillation.

In addition, women have longer QT interval to begin with and when exposed to drugs that prolong the QT interval, their QT interval prolongs even more, placing them at a much higher risk for the development of torsade associated with QT prolonging drugs and that's true for just about every drug that's been studied that has an effect on IKR, for example.

And then finally, and unfortunately, women have been grossly under represented in clinical trials, including trials of atrial fibrillation. As you'll see in this package, women are very well represented and as Dr. Raczkowski already pointed out to you, there are separate trials in women within this data set that you'll see today.

There was a good deal of

discussion yesterday about rhythm versus rate control and I'll just give you my perspective on this because I think it's a lot like the Miller Lite commercials, you know, it tastes great, less filling. There's truth to both. The truth of the matter is that in real clinical practice those of us who see lots of patients with atrial fibrillation individualize their care. And so there are patients clearly as you heard this yesterday from several of the panelists, there are patients who are very well served with rate control and anticoagulation. But there's a sizeable percentage of individuals who are not well served with that strategy. And we sometimes refer to these people as refugees because they get trapped in practices where primary care physicians have the incorrect impression that they can be managed only with rate control. And they're highly symptomatic. They finally find their way out of the practices into some cardiologist's office

somewhere who says well, maybe that's not the right thing. Maybe we should think about some other strategy for you.

So unfortunately, what's happened with these rate versus rhythm control clinical trials is there's been a gross over-extrapolation of the results to patients who are very, very unhappy with the idea of being in atrial fibrillation. I think you heard that yesterday from Mr. Simon.

And that really resonated yesterday, Mr. Simon, because I think it's really true that we underestimate the burden of the symptom state on patients and how badly patients feel when they're in atrial fibrillation.

It also is encouraged the under treatment of patients such as young people and one of the other things I think we need to keep very strongly in mind is we don't know the implications of atrial fibrillation for 30 years. The rate versus rhythm control

strategy studies follow patients for three or four years. What is 30 years of atrial fibrillation mean to somebody's ventricle and atrium. We simply don't have that information. And so we're very, very concerned about younger patients as well.

Now there are strong limitations in the current therapies we have available for atrial fibrillation. I think Chris did a very nice job yesterday in pointing out many of the limitations that we face in our current therapeutics. We have drugs that really -- I'm sorry, let me go ahead for a minute.

We have drugs that simply don't have the kind of efficacy that we would appreciate. Non-pharmacologic approaches such as pulmonary vein isolation or ablation procedures are not applicable to a large segment of our patients and even though they get a lot of press and we spend a lot of time talking about them, the fact of the matter is that we really don't have good evidence that

9794f29f-afdd-43a9-98b8-c39d54484326

these can be applied to a large segment of the population. And all of these things have very important safety concerns.

And remember that pursuing whatever strategy we do in atrial fibrillation does not obviate the need for repeated cardioversions or anti-coagulation.

I want to make it very clear as well that no matter how you make a decision to convert somebody from atrial fibrillation to sinus rhythm, there is always the concern that one may stun the atrium and predispose patients to the development of thromboembolic events. One of the things that I sensed yesterday was a bit of point of confusion. You stun the atrium no matter how you convert somebody from atrial fibrillation to sinus rhythm whether it's done pharmacologically or electrically, and so the rules that have been put into place for anti-coagulation and the transesophageal strategy hold as much for pharmacologic treatments as they do for

electrical therapies, no matter when those things are carried out.

We believe that restoration of sinus rhythm, in fact, does have a premium and I think you heard yesterday that there's very strong evidence that you can provide symptom relief in patients promptly with conversion to sinus rhythm.

One of the things we heard yesterday was that there was a concern about the timing of converting patients from atrial fibrillation to sinus rhythm and the idea that perhaps it would be a good idea to wait until patients spontaneously converted. I think that's a somewhat slippery slope for several reasons. Number one, when patients have nuance of atrial fibrillation, especially the elderly, and they convert from atrial fibrillation to sinus rhythm, we have a grave concern that those patients may have offset pause and offset pause after atrial fibrillation are associated with syncope. And

so many of our patients who have atrial fibrillation, especially during their first episodes, if unobserved during spontaneous conversion may be at risk. So sending them home and waiting 24 hours may not necessarily be an easy strategy for those individuals.

Likewise, when we see especially again elderly patients who have conduction disease, and we administer a rate control drug to those individuals, we can't send them home because we don't know how they're going to respond. They can respond inadequately with poor rate control or they can over-respond with a very profound negative dromotropic response. So watchful waiting is something that maybe you want to pursue some times, but you have to be very careful about advocating that as a global strategy because patients may not do well with that.

And there are things in the slide that I would not want to try to defend because as you heard yesterday, we don't have any

evidence that restoring sinus rhythm or maintaining sinus rhythm in patients with risk factors for thromboembolic events can warrant discontinuation of anti-coagulation. And that counts for ablation as well as it does for anti-arrhythmic drug treatment. I know there's a lot of ablationists that dangle that carrot out in front of the stick and patients say well, if I'm having an ablation procedure and I'm not going to be anti-coagulated, if they have risk factors, we don't have evidence that that's the case.

Where this may occur and it was stated yesterday, if you have patients who do not have risk factors for thromboembolic events and are converted to sinus rhythm after a period of observation, yes, they may have their anti-coagulation discontinued, but that's really the only place where that can occur.

And then finally, on this slide, I want to make another point that I made

yesterday, and I think is very important and that is we should not think of electrical conversion and pharmacologic conversion as competing strategies. They are complementary strategies. And frequently, in our clinical practice we use them in that way. That is, we may try a drug and if the drug doesn't work we may then go on to electrical conversion, and as you saw yesterday, in Chris Granger's presentation, there are data to suggest that some drugs may actually facilitate conversion of atrial fibrillation and ibutilide happens to be one of those agents.

Now the last thing I'll talk about and I'll try to wrap this up quickly, there are two major strategies that we've discussed over the last day for conversion of atrial fibrillation to sinus rhythm. One of them is electrical conversion. It's just very complicated because electrical conversion is extraordinarily effective. The use of biphasic wave forms is associated with an

efficacy in excess of 90 percent conversion rates, at least for a short period of time in atrial fibrillation.

One of the things I think you need to be very aware of is that if you cardiovert patients who are not receiving an anti-arrhythmic drug, and do not have an anti-arrhythmic drug in their system at the time that you cardiovert, the incidents of IRAF immediate or early recurrence of atrial fibrillation is as high as 30 percent in the first 24 hours after cardioversion. So it is not a durable treatment effect in patients who are untreated. Where we use cardioversion much more frequently in patients who have already received an anti-arrhythmic drug, either intravenously or orally, in that situation we have confidence that the effect will endure.

And you heard lots yesterday about the expense, the logistics, the idea that it's difficult to cardiovert patients to bring

anesthesia to the table, to have patients who are not postprandial, all those issues are real issues in implementing electrical cardioversion to clinical practice. And then the final point is it is not a free ride. Electrical conversion is associated with a fairly high rate of sometimes annoying, but whenever I say it's annoying I always try to put that in perspective because patients don't think it's annoying to have a skin burn. A skin burn is a really nasty thing after a cardioversion for a patient. And that's not infrequent after electrical conversion.

And for that reason, patients are not wild about the idea of being put to sleep and being shocked. You can get them to do it, you can talk them into it. After it's done they'll sometimes say well, gee, Doc, that wasn't nearly as bad as I thought it was going to be, but it's not that easy to convince them to have it. And if you give them the choice, if you give them an even choice between well,

we can try a drug first before we electrically convert, I can tell you almost 100 percent of the time they're ready for the IV.

So pharmacologic therapy. This is where it really gets complicated because as you heard yesterday we simply don't have the proper tools for this. There are not enough drugs available for this indication. The drugs that we have and that we use are used off-label almost always. IV amiodarone, as I said yesterday, is the most frequently employed drug and the only drug that has this label is ibutilide and none of us are particularly wild about the idea of using ibutilide. Having said that, one of the big reasons why people like to use IV amiodarone and I think Mike asked me this yesterday, is because there is a hook and maybe it was Bob. There's a book that if you use IV amiodarone you can go to oral and the reason why that's not such a bad deal is because you do get around this problem of immediate recurrence

because they are drug-loaded.

So the use of an IV drug prior to electrical conversion is not a bad deal. It may not be what you envision as being this magical thing that happens in the emergency room where it's like giving adenosine for SVT, it's not quite that simple, but it may set you up for better success for a subsequent electrical conversion.

Obviously, we need to take into account when we talk about using pharmacologic drugs what has the patient been treated with to that point in time, both in terms of AV nodal blocking drugs as well as membrane active drugs. So this becomes a very important consideration and sometimes a limitation to pharmacologic therapy.

So my last slide is -- what I tried to crystallize here is what I believe is the unmet medical need. I'm not saying that anybody has a drug that fulfills all of these qualifications and I don't think that that

would be a reasonable expectation, but this is what I'd like. I'd like to have a drug that has well-defined efficacy and safety profile for all the patients that I want to treat, not just men and women, but other subgroups as well. I'd like to have a drug that had a well-defined dose that I knew was going to work or at least I had some kind of an idea that it was going to work and I had some idea of what the downside of that dose might be.

I'd like a drug that has relatively simple kinetics. I don't really want to think about all the drug interactions if I can get around it. I really do agree with the FDA wholeheartedly that durability of effect is an extraordinarily important principle. One minute of atrial fibrillation I don't really care about. But if you can get me out to 24 hours I'm pretty happy about that.

Utility of atrial fibrillation for longer duration would be a great thing to

9794f29f-afdd-43a9-98b8-c39d54484326

have. That may not necessarily be something we can obtain with current pharmacology. And an ability to use it in patients that have structural heart disease, not necessarily really severe heart disease. I heard a lot of discussion yesterday about severe heart failure. I don't use pharmacologic therapy in severe heart failure. That's crazy. You don't want to do that. We cardiovert electrically or we just rate control our very severely sick patients, but I'd like to have a drug available that I know that I can use safely in patients that have the kind of heart disease that most of my AF patients have which is some coronary disease, some LVH, maybe a mild case of left ventricular dysfunction, but not severe.

So what I would ask you to do over the next hour or so as you hear more of these presentations, and I'll come back later and we'll do a little scorecard, is keep track and see whether you think that the drug you're

going to hear about today fulfills some of these qualifications and fulfills an unmet medical need.

With that, I'll welcome Dr. Matthias Straub to the podium who will spend some time telling you a lot about the efficacy and safety of intravenous tedisamil.

Thanks for your attention.

DR. STRAUB: Good morning, Mr. Chairman, Advisory Committee, FDA representatives, ladies and gentlemen. My name is Matthias Straub. I'm vice president of the Global Clinical Development Department at Solvay Pharmaceuticals.

In the beginning, I will make a statement on the key results of the clinical pharmacology studies and the present rationale of the dosage regimen used. I will also give an overview about the clinical development program and about the individual study results of the controlled clinical trials. This will be followed by a review of the integrated

study analysis for the primary efficacy parameter and I will conclude with efficacy conclusions.

Tedisamil is a Class III anti-arrhythmic drug. It has a mild heart rate lowering effect, but it does not substantially induce serious bradycardia. I'll make a point about that. Furthermore, our data show that tedisamil is hemodynamically neutral with respect to atrial and ventricular fibrillation with atrial and ventricular function with the exception of an increase in systemic vascular resistance.

Tedisamil's pharmacokinetics is linear and it's not affected by gender, age, or congestive heart failure. The elimination half-life is 4.5 to 6.9 hours.

Tedisamil is almost exclusively eliminated as unchanged drug by the renal routes. In subjects with mild to moderate renal impairment tedisamil's clearance decreases but Cmax is not affected, therefore

dose adjustment in subjects with mild to moderate renal impairment are not needed for single dose short-term infusions.

Metabolism of tedisamil is very limited. There is no in vitro evidence of P450-mediated metabolism. Furthermore, tedisamil is not a substrate for sub 2D6, but it's a potent inhibitor of 2D6, therefore pharmacokinetics of tedisamil are not effective in patients receiving P450 inhibitors. In addition, there is no effect of P450 genotypes on the pharmacokinetics of tedisamil.

In the first Phase II study, doses of 0.16 milligram per kilogram body weight or .24 and placebo were conducted using a 10-minute infusion regimen in a total of 26 subjects. There were no cardioversions observed. This study was discontinued due to slow recruitment and weak efficacy.

For the next Phase II studies, the infusion time was adapted to a two-step

infusion process with half the dose applied in the first 10 minutes and the other half of the dose applied in the remaining 20 minutes. The first 10 minutes were needed to be maximally controlled with low variability to reach Cmax. This excluded short-term bolus injection as an alternative because we assumed high variability of a freely-administered bolus intravenously.

The regimen was modeled using computer simulation techniques to broaden the AUC of the plasma concentration profile to allow the cardioversion to occur. The goal was to achieve stable QT values over at least 30 minutes. Also, Cmax should not be increasing beyond the predicted level of plasma concentrations to allow for a safe administration.

The goal was that a QT value should not exceed 550 milliseconds in the majority of the patients.

In summary, our intent was to

build a dosing scheme that achieved plasma levels rapidly so that cardioversion can safely occur, but also that one doesn't cause uncontrolled Cmaxes causing TdPs.

This slide shows the evolution of the plasma concentrations over time. You see here at the left hand, the plasma concentrations in nanogram per milliliter and here is the time. And you see here the QTcB in milliseconds. That shows controlled rapid increase in plasma concentrations with the sustained QTcB over two hours. This 30-minute infusion regimen was shown to be well tolerated in healthy volunteers and was the dosing regimen further used in Phase II studies and in all subsequent Phase III studies.

The next study conducted was the Phase II proof of principle study. It used does of 0.32 milligram per kilogram body weight; 0.48 milligram per kilogram body weight and placebo. It was using the 30-

minute infusion regimen and recent onset atrial fibrillation or flutter of less than 48 hours duration.

The results for this proof of principle study 2.107 are given for the primary efficacy parameter for atrial fibrillation. The efficacy parameter was the percentage of subjects who converted to normal sinus rhythm at any time within 2.5 hours after the start of the study drug infusion. The conversion rates were 57.1 percent under dose of tedisamil 0.48 and 46.2 percent as a dose of 0.32 milligram per kilogram body weight, 8.7 percent conversion of placebo. The results were the placebo were highly statistically significant.

Overall, the Phase II data did not indicate a detrimental effect of tedisamil on the defibrillation energy needed in subsequent DC cardioversions as for instance in the Study 2.107 monophasic defibrillation threshold energy required appear to be lower in

tedisamil-treated patients than in placebo-treated patients. The results went in the same direction for biphasic energy.

Phase III studies began in November 2002 using doses of 0.3 milligram per kilogram body weight up to doses of 0.64 versus placebo. However, these studies were suspended in March 2003 following several reports of torsades in female subjects. A thorough investigation revealed that the arrhythmic events in female subjects were associated with doses of 0.48 milligram per kilogram body weight or higher. We had reviewed the available data at that time point, had consultations with the FDA and the MHRA and restarted the program thereafter with the dose finding strategy separated by gender.

Subsequently, the study 3.112 investigating doses of 0.32 milligram per kilogram body weight up to 0.64 and placebo was amended to enroll only male subjects. In addition, two other gender specific dose

studies were conducted, study 3.114 investigating 0.16, 0.32, and 0.48 versus placebo and 3.117 investigating 0.48 versus placebo.

In females, two gender-specific placebo control studies were done: 3.116 investigating 0.24 and 0.32 versus placebo; and 3.118, 0.32 versus placebo.

All Phase III studies were multi-centered, randomized, placebo-controlled, parallel-dose finding studies or dose confirmation studies. All had the same basic design. The only differentiation was that the tedisamil doses tested were differing in the gender of the patients.

There was a screening period of up to 48 hours. Patients with symptomatic atrial fibrillation or flutter of a duration of three hours to 45 days were administered as a first -- with a first or recurrent episode were hospitalized and then they were randomized to receive tedisamil or placebo using a 30-minute

infusion regimen.

There was a 24-hour observation period in which telemetry, Holter, ECGs, pharmacokinetic investigations and adverse events were recorded. And finally, there was a four-week follow-up period with the assessment of adverse events.

In the 24-hour observation period, patients were not allowed to take any other anti-arrhythmics. Subjects were hospitalized and monitored for 24-hours by Holter ECG. That Holter ECG was started 10 minutes before the infusion and was analyzed centrally to identify the first conversion to normal sinus rhythm and to collect info on the maintenance of normal sinus rhythm over 24 hours.

The Holter recordings were also analyzed for safety. Ventricular tachycardia events were coded by prespecified definitions and adjudicated by the Adjudication and Oversight Committee.

Patients had to have documented

9794f29f-afdd-43a9-98b8-c39d54484326

atrial fibrillation or flutter. They had especially to be symptomatic with episodes of a duration of three hours, but not more than 45 days, either as a first or as a recurrent episode. They had to be hemodynamically stable and at least 18 years of age.

Key exclusion criteria were congestive heart failure, Class IV; history of life-threatening ventricular arrhythmias including TdP; myocardial infarction; severe renal impairment; congenital long QT syndrome; QTc interval more than l470 milliseconds; concurrent treatment with anti-arrhythmic drugs, except for digital, diltiazem or beta-blockers; sick sinus syndrome; and need for internal or external pacemaker.

The baseline characteristics of the overall patient population, the clinical program showed that the patients were predominantly Caucasian. In comparison to male patients, there was a higher proportion of female patients older than 65 years of age.

In male patients, up to 32 percent had Class II congestive heart failure. Up to four percent had Class III CHF. In female patients up to 46 percent had Class II and Class III, 7.2 percent.

Of the 28 percent of patients presented with mild to moderate renal impairment, the incidents in female patients was somewhat higher than in males. And in male patients, a slightly higher proportion of patients had a duration of episode of less than 48 hours, whereas female patients had predominantly episodes of more than 48 hours in duration.

The primary efficacy parameter was the percentage of subjects who converted to normal sinus rhythm for at least 60 seconds at any time within a 2.5 hour period after the initiation of the infusion of the study drug.

The primary efficacy sample was defined a priori in the individual studies. A modified AFib ITT sample was defined as all

patients randomized, but excluding patients not receiving study drug treatment or converting before their start of the infusion or with no post-baseline efficacy data. Further exclusions from the primary analysis were DC cardioversions within 2.5 hours from the start of the infusion.

We found these were reasonable exclusions. Also, the number of patients excluded were very low. In addition, we have conducted analysis excluding all patients -- including all patients and came to similar results.

Secondary efficacy parameters were timed to first conversion and the percentage of patient satisfying the primary endpoint meaning the conversion within 2.5 hours and a normal sinus rhythm at 2.5 hours; a normal sinus rhythm at 24 hours; and a normal sinus rhythm at hospital discharge. Other secondary efficacy parameters were analyzed using the integrated efficacy safety database and that

was the percentage of subjects who converted within 2.5 hours and remaining a normal sinus rhythm at 24 hours.

The following I'll present the efficacy results from individual studies in the Phase III program. The first study you'll see here the primary efficacy parameters reported for AFib male patients. Received 23 percent converted on the dose of 0.32; 52.9 percent converted under a dose of .48; and 67.4 converted under a dose of .64.

In the next study, 29.4 percent converted on the 0.32; 31.1 percent on the .48; and we had in the final study 29.2 percent under the dose of .48. Statistical results for each of those comparisons were highly statistically significant, except for a dose of 0.16 in male patients.

In female patients, we had conversion rates between 9.4 percent and 21.5 percent. A second study confirmed conversion rate of 17.9 percent versus placebo. Only one

result was not highly statistically significantly different and that was the dose of 0.24 milligram per kilogram body weight.

This figure graphically shows the placebo corrected point estimates and confidence intervals associated with the confirmatory analysis by individual study for the dose -- and dose for the male studies. Across the three predominantly male studies, a statistically significant increase in the rate of conversion to normal sinus rhythm within 2.5 hours was observed in doses of tedisamil 0.32 and higher. Doses of lower than 0.32 were not significantly different.

In female patients, in the two studies conducted, tedisamil at a dose of 0.32 milligram per kilogram body weight significantly increased the rate of conversion within 2.5 hours. Again, 0.24 milligram per kilogram did not differ.

In the sensitivity analysis, all randomized subjects are included. Those

subjects who converted within 2.5 hours are counted as successes regardless of whether they also receive DC cardioversions or not. Also, subjects who converted before the initiation of infusion are counted as successes.

Just remember that there were also some difference mentioned about the correct patient's efficacy sample in the FDA briefing book. You might hear some different definitions from the FDA later. Here is what we did. On this slide, you can see an example for the comparison of the formal ITT analysis in Study 2.3112 to the modified ITT analysis given in the dossier. The results are comparable.

To sum up, there were five Phase III multi-center randomized, double-blind, placebo-controlled studies evaluating the efficacy of tedisamil. These five studies included two dose ranging studies and one confirmatory study in male subjects and one

dose ranging and one confirmatory study in female patients.

All studies met their primary objective demonstrating efficacy in a confirmatory setting. The exclusion of studies in the modified ITT versus the formal ITT analysis did not have any impact on the efficacy findings.

Furthermore, there were subgroup analyses performed. These were performed on the basis of the type of arrhythmias, the duration of the episodes, less than 48 hours and more than 48 hours. Age groups of less than 65 years, more than 65 years; meta-blocker treatment, yes or no; New York Heart Association classification I versus II and III; episodes either as first or recurrent; and creatinine clearance of less than 60 per minute or more than 60 milliliter per minute.

The results confirmed efficacy in all subgroups tested at a dose of 0.48 milligram per kilogram body weight in male

patients.

Tedisamil showed the same evidence in female patients at a dose of 0.32 milligram per kilogram body weight with the exception of patients with atrial flutter.

An analysis was performed in patients with a duration of episode of 3 hours to 45 days, but also for patients with a duration of episode between 3 hours and 7 days for males and females, and 8 days to 45 days as indicated here. The results confirmed efficacy in all subgroups tested except for the window of 8 days to 45 days at a dose of 0.32 milligram per kilogram body weight in female patients, what you see here.

This slide shows that the patient with the duration of episode of up to 7 days treatment provides substantial evidence of conversion to normal sinus rhythm. And male patients receiving a dose of .48 milligram per kilogram body weight, the proportion of patients converting to normal sinus rhythm

9794f29f-afdd-43a9-98b8-c39d54484326

within 2.5 hours was 46.4 percent versus 9 percent on the placebo and in female subjects there were 26.3 percent versus 5.5 percent on the placebo.

As indicated earlier, a secondary efficacy parameters were focused on the durability of the effect and on whether or not the drug would convert patients to normal sinus rhythm rapidly. This was measured by the percentage of subjects converting to normal sinus rhythm within 2.5 hours and remaining in normal sinus rhythm at 24 hours and normal sinus rhythm at hospital discharge. Rapid conversion was evidenced by the time to first conversion.

The results in male patients showed that at those at .48 milligram per kilogram, of the 59 subjects who cardioverted to normal sinus rhythm within 2.5 hours, 53 remained in normal sinus rhythm at 24 hours, that is, 89 percent. Seventy-nine percent were in normal sinus rhythm at hospital

discharge.

This comparison looks at data from those patients who converted within 2.5 hours following start of infusion. It looks at whether or not those patients were remaining in normal sinus rhythm at 24 hours. This was discussed and agreed with the FDA.

This is not a comparison of the status of being or not in normal sinus rhythm at 24 hours. Such analysis was not our intent as the efficacy at 24 hours is confounded by other interventions such as cardioversions beyond the 2.5 hour time point.

In female subjects at a dose of 0.32 milligram per kilogram body weight, 37 percent or 57 patients converted to normal sinus rhythm within 2.5 hours. Thirty-two patients, that is 86.5 percent, remained in normal sinus rhythm at 24 hours. And 81 percent of patients were in normal sinus rhythm at hospital discharge.

Conversion to normal sinus rhythm

occurred in less than 30 minutes from the start of the infusion. The median time to conversion to normal sinus rhythm for males showed a dose response with time decreasing as dose increased.

In conclusion, tedisamil is effective at restoring normal sinus rhythm in subjects with atrial fibrillation and flutter of a duration of 3 hours to 45 days. Tedisamil's effect was rapid and was sustained. The effect was robust across subgroups of interest and it was robust across other methods of handling exclusions from the ITT.

Tedisamil's safety. In the following, I will describe the tedisamil exposure, it's adverse events including total adverse events, cardiac adverse events and serious adverse events, including deaths. I will also talk about adjudicated events from Holter monitoring which need to be separated from adverse events reported by the

investigators. Furthermore, I will address the recommended monitoring window for the follow up and I will finally talk about the dose selection and recommendation.

Tedisamil is intended to be administered as an intravenous infusion. On this slide the number of subjects who have received an infusion of IV tedisamil. A total 1137 subjects were exposed to tedisamil intravenous, among them, 931 patients with atrial fibrillation and flutter. Safety data from 931 AFib/flutter subjects who were exposed to a single infusion of tedisamil were included in an integrated safety data set, along with the data from 470 patients exposed to placebo in the same studies.

In the integrated safety data set, the tedisamil group consisted of 759 males, that is 528 tedisamil patients and 231 placebo patients, and 642 females, that is 403 tedisamil-treated patients and 239 placebo patients. Subjects were almost exclusively

Caucasian. The female population tended to be older by about eight years, more likely to have more severe congestive heart failure, and had a tendency for a higher proportion of subjects with creatinine clearance of less than 60 milliliter per minute.

It is important to consider that adverse events are collected and reported over a four-week follow up period and do not represent only 24 hour data. This analysis was performed to appropriately follow up the patients and to be able to make also a statement on adverse events which might happen as a result of various treatment options following cardioversion of tedisamil such as DC cardioversion and introduction of any other anti-arrhythmics after 24 hours.

In general, the overview of the results indicate that the incidents for deaths, serious adverse events, treatment emergent serious adverse events, and adverse events leading to study discontinuation and

severe treatment emergent adverse events appear comparable between male patients treated with 0.48 milligram per kilogram and placebo and female patients treated with 0.3 milligram per kilogram and placebo. In contrast, emergent adverse events appeared to be more frequent in tedisamil treated patients.

In male patients, in general, treatment emergent adverse events were reported with similar incidents in tedisamil and placebo-treated patients with the exception of gastrointestinal disorders, general disorders and administrative site conditions, nervous system disorders, vascular disorders and cardiac disorders. The cardiac disorders are of special interest and they are discussed later.

The most frequently reported patterns of treatment emergent adverse events associated with tedisamil were hypoesthesia oral, paresthesia circumoral, and paresthesia

oral. Although hypertension was observed in very few patients receiving tedisamil, the reported rates are comparable with placebo. This is supported by data showing that the hemodynamic effect of tedisamil includes an increase in systemic vascular resistance with slight increases in blood pressure, rather than blood pressure decreases.

Further frequent treatment emergent adverse events were general disorders and administration site conditions such as injection site burning or injection site pain.

In female patients, the data were similar with again hypoesthesia and paresthesia being the most frequent treatment emergent adverse events.

Hypertension and orthostatic hypotension were not relevantly different from placebo; 3.3 in the placebo, 2.2 in the 0.32.

Injection site reactions such as injection site burning or injection site pain were also reported in female patients as one

of the most important patents for treatment emergent adverse events following tedisamil in treatment.

In many patients, tedisamil groups had a higher percentage of subjects with treatment emergent adverse events of cardiac disorders as compared to placebo. Cardiac disorders included also bradycardia, sinus bradycardia or bradyarrhythmia with incidents of slightly more prominent under tedisamil versus placebo and ventricular tachycardia.

However, overall, the data did not show high incidents of bradycardia related adverse events compared to placebo. Overall, our data support that tedisamil's pharmacodynamic effects includes a mild slowing of heart rate, rather than a substantial induction of bradycardia.

No torsade de pointes were reported as treatment emergent adverse events from the investigator. This is important when we will later talk about the Holter findings.

9794f29f-afdd-43a9-98b8-c39d54484326

The incidents of ventricular tachycardia were reported as treatment at adverse events in 12.6 percent of patients treated with 0.48 milligram per kilogram body weight and 6.9 percent treated with placebo in female subjects -- in male subjects.

In female patients, the data were similar with tedisamil groups having a higher percentage of subjects with treatment emergent adverse event of cardiac disorders. Bradycardia was reported with 5.8 percent versus 3.3 percent on the placebo. There were no treatment emergent adverse reported on torsade de pointes under the dose recommended of 0.32 milligrams per kilogram body. Again, this will be important to consider when we describe the events from the Holter recordings.

The incidence of ventricular tachycardia reported as treatment emergent adverse events was comparable in placebo and tedisamil treated patients at a dose of 0.32

milligram in female subjects.

With respect to treatment emergent serious adverse events in male patients, these incidents were overall reported by a similar percentage of subjects in the tedisamil and placebo groups. On two occasions bradycardia were reported as serious adverse events in tedisamil treated patients. There was none on the placebo and male patients. And in female patients treatment emergent serious adverse event again were reported by a similar percentage, again a slightly higher proportion of patients were reported with cardiac disorders and two placebo patients this time were reporting bradycardia, serious adverse events where there was no case under tedisamil.

I said that there were four treatment emergent serious adverse events with bradycardia. In males, these were two serious adverse events. In the first case, there was one patient with atrial flutter who received

0.48 milligram per kilogram tedisamil and experienced significant bradycardia with subsequent placement of a pacemaker. The patient was discharged without a sequelae and the event was judged possible by the investigator.

In the second case, there was a patient with atrial fibrillation again who received .48 milligram per kilogram body weight. The patient was discharged one day later. The serious adverse event of bradycardia however was reported 15 days after the infusion. The event was judged unrelated to study treatment. Subsequently, the patient had a pacemaker implanted without complication.

In female patients, again, two serious adverse events were observed. Both patients received placebo and were reported as serious adverse events. One patient received a pacemaker subsequently.

In male subjects at a dose of 0.48

milligram per kilogram body weight, the incidents of patients with treatment emergent adverse events leading to study discontinuation was infrequent, but with 1.9 percent was slightly higher than under placebo with .9 percent.

At a dose of .48 milligram per kilogram, one patient was discontinued due to bradycardia with a percentage of .5 percent and QT prolongation was the other reason for discontinuation in three cases. Hypotension was not reported as reason for discontinuation at a dose of .48 milligram per kilogram per body weight.

In female patients at a dose of 0.32 milligram per kilogram body weight, the incidence of patients with an adverse event leading to study discontinuation was 2.2 percent, slightly higher than under placebo with 1.3 percent. At a dose of 0.32, adverse events leading to study discontinuation were infrequent and did not show a specific adverse

9794f29f-afdd-43a9-98b8-c39d54484326

event pattern, but it included bradycardia with one case of .4 percent.

Again, no patient was discontinued for hypotension at a dose 0.32 milligram per kilogram, while there was one patient following placebo treatment.

Thromboembolic events are frequent observations in patients with atrial fibrillation and flutter, although the reasons for the incidents may be multi-factorial. These adverse events are covering a treatment follow-up period of four weeks. We have analyzed the incidents of thromboembolic treatment emergent adverse events and found a homogeneous distribution over the various doses tested with no apparent adverse event pattern, although one stroke was reported as a treatment emergent adverse event under 0.48 milligram per kilogram tedisamil, while there was none on the placebo.

Of note, all events occurred in patients not converting, except one male

patient with arterial limb thrombosis and two myocardial infarctions.

Also, in female subjects, we have analyzed the incidents of thromboembolic treatment emergent adverse events and found a homogenous distribution over the various doses tested. No apparent adverse event pattern was observed, although one stroke was reported as treatment emergent adverse events on .32 milligram per kilogram body weight, while there was none on the placebo.

Also, two acute myocardial infarctions were reported under treatment emergent 0.32 and none on the placebo. All events occurred in patients not converting, except one female patient with cerebral vascular accident.

Nine deaths were reported in the tedisamil IV program. Overall, the deaths were equally distributed with 0.6 percent of deaths occurring in patients treated with tedisamil and 0.6 percent of deaths occurring

in placebo patients.

The incidents in male patients was 0.9 percent following placebo treatment, while no patient died following 0.48 milligrams. In female patients, the incidents was .4 following placebo treatment, while it was 0.9 percent following 0.32 milligram per kilogram.

Three deaths occurred in male patients, two on placebo and one on tedisamil. The one case following tedisamil treatment was a myocardial infarction eight days after the initiation of study drug infusion. There were six cases in female patients, one of which was on placebo.

From the remaining five cases, four cases were considered unrelated to tedisamil application: pneumonia, pulmonary embolism, stroke, acute myocardial infarction, pneumonia, all occurring late in the game except pulmonary embolism which occurred on day one.

Finally, there was one case

considered unlikely to be related to study drug treatment, cardiac arrest on day three following study drug treatment by the investigator. However, a connection with tedisamil treatment in this case cannot be excluded.

This case was Patent 43001 who had a diagnosis of atrial fibrillation with recurrent ventricular tachycardia with hypotension, coronary artery disease with an old interior wall MI, essential hypertension, and rheumatic heart disease with mild mitral regurgitation. In our view, this patient was the prodigal violator in two cases. First of all, this patient was having a diagnosis of atrial fibrillation with recurrent VT as diagnosis; and second, this patient had a rheumatic heart disease with valvular heart disease.

This case occurred in connection with infusion discontinuation due to bradycardia and asystole. The patient was

subsequently receiving CPR, was intubated and was receiving ventilation treatment. Two days after the infusion, the patient was extubated and reverted to atrial fibrillation. Thereafter, a second attempt was taken to cardiovert the patient this time with amiodarone. Bradycardia reoccurred and despite pacing efforts, the patient subsequently died.

In our opinion, this patient shouldn't have been included because connection with rheumatic heart disease, she was probably suffering from a sick sinus and was likely in need of a pacemaker which was an inclusion criteria in our studies. Although this could not be further substantiated with data.

The safety of tedisamil study program was supervised by the Adjudication and Oversight Committee, the data safety and monitoring board for the tedisamil program.

As part of each study protocol, at

24 hour Holter ECG was started 10 minutes before the start of the study drug infusion. The Holter tapes were sent to a specialized CRO for ECG analysis and were then evaluated according to the specific Holter analysis definitions.

All events of three or more abnormal atrial or ventricular complexes with a rate of more than 100 beats per minute were defined as single episodes of ventricular tachycardia. Events were evaluated for several primary categories and then shipped to the AOC members for the adjudication.

The events were mainly categorized by being either monomorphic or polymorphic, sustained or nonsustained or torsade-like. It's important to consider that the incidents of the events in the following tables do not represent adverse events reported by the investigator, but they do represent adjudicated findings from Holter recordings. This differentiation is important because not

all episodes of three beats of adjudicated VTs from Holter recordings were reported as adverse events. Holter events were frequently silent, nonsymptomatic episodes of ventricular tachycardia and were therefore not observed and reported by the investigators.

By using the adjudication and oversight events from Holter recordings, we were able to very accurately describe the risk for torsade in our development program.

The incidents of various types of ventricular tachycardias are summarized in this table for male patients. The incidents of VT at a dose of .48 was slightly higher than in the placebo group with 31.4 versus 25.8 percent. Monomorphic runs were slightly more common than polymorphic runs in both tedisamil and placebo groups with the vast majority of the VTs being nonsustained. See 21.3 nonsustained monomorphic versus 18.7 on the placebo.

Polymorphic VTs are of particular

interest. The incidents of polymorphic nonsustained VTs was 16.9 percent on the .48 versus 14.7 on the placebo. Sustained polymorphic ventricular tachycardias were experienced by two tedisamil patients, one on the .48 and one on the placebo.

In female patients, the incidents of ventricular tachycardia as a dose of 0.32 was slightly higher than in the placebo group with 17.8 percent versus 15.3 percent on the placebo. Again, monomorphic runs were slightly more common than polymorphic runs in both study and placebo groups with the vast majority of ventricular tachycardias being nonsustained.

The incidents of polymorphic nonsustained ventricular tachycardias was 12 percent and 10 percent on the placebo. Sustained polymorphic ventricular tachycardias were experienced with two tedisamil-treated female patients and one case on the placebo.

In male patients, treatment-

related adjudicated torsade-like events occurred closely related to the infusion regimen. Drug-related events occurred maximally 48 minutes after the start of study drug administration. The one case, 18 hours after the infusion, after the start of the infusion we do not consider drug-related. This is important to consider when defining the window of observations for tedisamil-treated patients later.

In female patients, treatment-related adjudicated torsade-like events again occurred closely related to the infusion regimens. Sustained events occurred maximally 30 minutes after the start of the infusion.

In males at a dose of .48 milligram per kilogram body weight, the incidence of adjudicated torsade-like events was .5 percent and .4 percent under placebo. On doses higher than 0.48 milligram per kilogram body weight, the incidence was 4.5 percent with a confidence in total between 0.9

and 12.5.

In female patients at a dose of 0.32 the incidence was .4 percent with a confidence interval of 0 to 2.5. On doses of higher than 0.32 milligram per kilogram body weight, the incidence was 9.1 percent with an upper confidence interval of 20.

Safety was assessed in sub-group populations including subjects with an age of more or less than 65 years with and without beta-blocking agents with and without renal impairment and with and without congestive heart failure. The number of patients with Class III heart failure was very limited, between 4 and 7 percent of the overall patient population. Thirty to 40 percent had Class II and 40 to 60 percent had Class I heart failure. Therefore, the safety subgroup of Class II-III, was reported together.

It makes no significant and clinically-relevant differences between tedisamil and placebo were observed in

subjects of less than 65 and more than 65 years of age. In subjects with Class I and Class II-III, again, no meaningful differences were observed between tedisamil and placebo. Also, no relevant differences were observed in patients with creatinine clearance of less than 60 milliliter per minute. For subjects not taking beta-blocker agents, a slightly higher rate of tedisamil treatment emergent adverse event related adverse events were occurring versus placebo, 64.3 versus 53.4 percent.

Again, similar results were obtained in female patients. No clinically-relevant differences were observed at the recommended dose. With subjects not taking beta-blocker agents, a slightly higher rate of treatment-emergent adverse events in tedisamil-treated female subjects was observed in comparison to placebo patients.

For serious adverse events, there was no clinically-relevant difference between

tedisamil and placebo observed for subjects of less than 65 years of age and more than 65 years of age. Again, no clinically-relevant difference between tedisamil and placebo was observed for Class I and Class II-III.

Finally, no relevant difference was observed for patients with creatinine of less than 60 or more than 60.

For subjects without concomitant and beta-blocker agents, tedisamil treated male subjects appear to have a slightly higher incidence of treatment-emergent serious adverse events in comparison to placebo subjects, 8.6 versus 2.7 percent.

No clinically-relevant differences between tedisamil and placebo were observed at the recommended dose and the incidence of serious adverse events in female patients.

Some words about the monitoring window. The recommended time for patient observation should not only be defined in our view under the consideration of the time

relationship between the potential occurrence of the torsade de pointes, but also by indirect evidence of potential precursors or risk factors for torsade de pointes such as prolonged QT or QTc.

This data generated in healthy volunteers shows that at the start of the two-step infusion regimen pharmacokinetic plasma concentrations steeply rise and then thereafter, quickly decline. With this first steep increase of QTc which is back to baseline at 2.0 hours after the start of the infusion regimen.

While the measurement of the QTc is significantly hampered in patients with atrial fibrillation which makes it very difficult to measure QT, the estimation of QTc changes in the arrhythmia program remained a challenge. Nevertheless, the ECG data showed that at a time point of 2.5 hours after the start of the infusion process in male patients, after a steep increase after 30

9794f29f-afdd-43a9-98b8-c39d54484326

minutes, the values already showed the significant decline in a clinically-relevant decrease of QTc at 2.5 hours.

Similar observations can be made in female patients. The ECG data show that 2.5 hours after the start of the study drug infusion, after steep increase of 24 -- after 30 minutes, we see a relevant decrease already after 2.5 hours.

During the clinical program, torsade-like events occurred within 48 minutes after the infusion start. One event occurred at 18 hours which was unlikely related to tedisamil. Also, within 2.0 hours QTc measurements returned to normal in healthy volunteers and the majority of the patients in atrial fibrillation and flutter have substantial reductions of QTc after 2.5 hours.

Based on the above, we are proposing an observation window for a minimum of two hours after the start at post infusion. However, we recommend that the patients who

9794f29f-afdd-43a9-98b8-c39d54484326

have not achieved normal QTc values by that time point, need to be followed up until their QTc has returned to normal.

Safety conclusions. Tedisamil's safety is supported by a substantial database involving 932 patients with atrial fibrillation or flutter with a balanced male-female exposure and a four-week follow-up period. Cardiac disorders are reported as most treatment emergent adverse events and treatment emergent serious adverse events. Adverse events and serious adverse events show an increase which is similar across all subgroups investigated, such as gender, age, NYHA classification, concomitant beta-blocker treatment and renal impairment.

The incidents of ventricular tachycardia as defined and adjudicated by the AOC Committee were slightly higher in the tedisamil group as compared with the placebo group. However, the vast majority of the events were nonsustained. They were silent

episodes and did not need cardiac intervention. Nor were they reported as adverse events.

Twelve cases of adjudicated torsade-like events were observed, 11 events following tedisamil treatment and one event following placebo treatment. In female patients at a dose of 0.32 milligram per kilogram body weight, the incidence was reported below one percent. The same applies for a dose of 0.48 milligram per kilogram body weight in male patients.

All DC cardioversions performed in patients with sustained arrhythmias were successful. They were resulting in normal sinus rhythm. With respect to dose selection, tedisamil has been proven to rapidly and effectively converting atrial fibrillation and flutter to normal sinus rhythm within 2.5 hours.

To optimize the risk-benefit ratio a gender-specific dose finding program was

conducted at a dose of 0.48 milligram per kilogram body weight in males and 0.32 milligram per kilogram body weight in females. Conversion with tedisamil is demonstrated in 34 percent of males and 18 percent of females for atrial fibrillation and flutter.

Lowering the dose of 0.48 to 0.32 would be significantly diminishing efficacy. Conversion is rapid and persistent for longer than 24 hours.

The most common treatment emergent serious adverse event were cardiac disorders, including pro-arrhythmic events. Of these ventricular arrhythmias and especially torsade de pointes are the most serious and they are potentially life threatening. The incidence of ventricular tachycardia was modestly elevated in the treatment group with majority of the events considered mild in intensity. Of note, all events of three or more abnormal and aberrant ventricular complexes with a rate of more than 100 beats per minute were defined

as single episodes of ventricular tachycardia.

At a dose of .48 in male patients, the incidents of adjudicated events was .5 percent and at a dose of 0.32 milligram per kilogram, it was .4 percent.

Doses of higher than 0.32 were associated with an increase of adjudicated torsade-like events in female patients.

To optimize benefit while minimizing the risk of torsade de pointes, the following doses are therefore recommended: 0.48 milligram per kilogram body weight in males; and 0.32 milligram per kilogram in females.

Thank you. I will now hand over to Dr. Earl Sands who will present the risk management plan.

DR. SANDS: Good morning, Mr. Chairman, members of the Advisory Committee, FDA representatives, ladies and gentlemen. My name is Earl Sands and I am the vice president of research and development and Chief Medical

Officer for Solvay Pharmaceuticals, Inc. Today, I will present the post marketing plan for tedisamil. We'll be discussing the RiskMAP first, followed by the Pulzium Observational Study.

The purpose of the RiskMAP is to optimize the benefit-to-risk balance by ensuring the product usage which is consistent with our data findings and the resultant prescribing information. Additionally, I will discuss pharmacal vigilance and drug safety actions specific to our program which will enhance the risk benefit during the usage of tedisamil.

Solvay employed a comprehensive development process involving all stakeholders who will participant in the prescribing and administration of tedisamil. Following an internal development process, we discussed our findings with physicians, pharmacists, and nurses for validation in both the U.S. and the E.U. This was an iterative process and

revisions were made to the program as we received feedback from potential users. It was important that we create a plan that would work in the real world and allow for the minimization of risk and the maximization of the benefits in a manner that would fit well into the current clinical practice and procedures.

The objective of the RiskMAP is to align the usage of tedisamil with the proposed prescribing label. Selection of the appropriate patient in the correct clinical setting where continuous cardiac monitoring is performed in addition to the gender-specific dosing and two-bag administration enhances the risk-to-benefit ratio.

Post infusion, the patient is monitored for efficacy and side effects in a setting where cardiac monitoring is continuous. The patient may be discharged at two hours from the start of infusion if the patient has demonstrated efficacy and the QTc

has returned to normal.

As we've heard earlier today, there are risks with the usage of all Class III anti-arrhythmic drugs. The Solvay RiskMAP addresses the most important causes of serious adverse events, most specifically, the potential for miscalculation or misadministration of the dose. The focus of the RiskMAP is on providing tools that enhance the proper dosing and administration of the product.

The Solvay RiskMAP provides for multiple tools to be utilized by the health care team to effectively mitigate risks associated with usage of tedisamil. Our plan focuses on three main aspects. One, our labeling which is the first line of communication is comprehensive, containing gender-specific detailed height and weight dosing information. Two, targeted education to the health care providers and proactive outreach during the prescribing and usage via

multiple tools which contain a reminder function. And three, tools distributed with each prescribed dose such as a physician checklist, an infusion bag sticker and an arrhythmia guide, QTc guide, dose guide and calculator, and an administration and monitoring guide. When taken together, these tools provide a comprehensive suite of information and reminders to guide health care professionals through the prescribing process. Examples of these materials are included in the appendices of your briefing package.

Let me show you two of these tools now. The cornerstone of the RiskMAP tools is the physician checklist. This step-by-step guide should be completed for each patient in which tedisamil is being considered as a treatment. The guide is comprehensive, starting with a list of inclusions and exclusions through the administration of prescribed dose with the resultant outcome. The checklist is to be made part of the

patient chart when the treatment is completed.

In addition, there is a color-coded gender-specific dosing chart. I'm showing you a portion of these charts right now; blue for males and red for females. Specific dosing is easily determined by identifying the weight and the height of the patient on the appropriate chart and choosing the dose at the intersection as demonstrated here. This chart is also included in the labeling.

In addition to the tools supporting the selection of the correct dose, successful and safe implementation of a two-step infusion is important to minimizing the risk of torsade. We've heard comments from the FDA and others about the potential to simplify the dosing regimen to minimize the risk associated with too rapid infusion. To this end, we are recommending that a two-bag administration regimen be adopted. The total dose would be made up in two infusion bags.

The first bag is administered over 10 minutes and then when the second bag is administered, the rate of the infusion is changed on the IV pump. This eliminates the risk of too rapid infusion in the administration of tedisamil.

As you can see, there is redundancy built into the major risk areas associated with the usage of tedisamil. The redundancy is deliberate and comprehensive. Solvay believes that the previously-described RiskMAP effectively mitigates the main risks that are associated with the administration of tedisamil.

Let's turn now to the Pulzium Observational Study or POST. This study is in addition to the hospital discharge record program which was presented in your briefing document. POST is a prospective, observational study encompassing 1200 to 2000 patients from approximately 120 geographically-diverse sites. We will collect and analyze demographic, prescribing, past

medical history, comorbidities, and adverse event data. We will be looking at efficacy and safety at 24 hours, monitoring concomitant meds and related treatments, and including whether additional cardioversion attempts were made.

This study is designed to generic real-world benefit-to-risk data.

The Pulzium Observational Study will generate periodic and real-time safety data that will enable us to confirm efficacy and safety in under-represented ethnic populations. We will also use this data to evaluate the receipt and usage of the RiskMAP materials.

The study will be under the direction of an independent drug safety monitoring board. The data will be evaluated quarterly at every 300-treated patients to assure timely analysis. The results will be shared with the FDA in concordance with the REMS criteria.

In conclusion, Solvay proposes a post-marketing plan which proactively addresses the known risks, a RiskMAP which is comprehensive, and has built-in redundancy to improve its effectiveness. The RiskMAP includes tools which are aligned with present clinical activities thus not creating a hindrance to usage.

Solvay is also committed to on-going evaluation to the RiskMAP and revisions as indicated. Additionally, the effects of the RiskMAP are to be evaluated along with our continued assessment of the benefit-to-risk profile in subpopulations in the Pulzium Observational Study.

Solvay believes the post-marketing plan will effectively mitigate the concerns related to the usage of tedisamil.

Thank you. I'd now like to invite Dr. Kowey to the podium.

DR. KOWEY: Thank you, Dr. Sands. So allow me to show you the slide that I

showed you at the end of my presentation and we'll briefly review some of the elements that I told you earlier as an electrophysiologist I'd like to see available in new compound.

Defined efficacy and safety profile. I think that you'll agree that the studies that have been performed to date have adequately defined what the efficacy and safety of this compound is, at least for the common adverse events.

Defined dosing and instructions for use. I also believe that the dose response has been adequately explored. Doses below the recommended doses don't work as well and doses above the recommended doses are associated with intolerable and very nasty adverse events.

The drug has very simple kinetics, without major concerns about patients who have either moderate renal impairment or hepatic disease. Clearly, durability of effect extends out to the 24-hour window and beyond.

A utility in atrial fibrillation of longer duration, clearly with a smaller magnitude of treatment effect as we saw yesterday for vernakalant. And efficacy and safety in patients with structural heart disease.

So the benefits of tedisamil is that it provides rapid persistent efficacy in the conversion to sinus rhythm defined by gender, with rapid conversion with durability of effect.

You've also seen that there is an absence of demonstrable hemodynamic, iteration in patients. In fact, we would not predict that this drug based on what we know about it pre-clinically would have a negative inotropic effect either in the atrium or in the ventricle. And as I pointed out earlier since drug therapy is frequently used in concert with electrical conversion, demonstration of a complementary approach and the fact that one does not interfere with the other is obviously of great clinical importance.

The drug is effective and safe across some of the subgroups that we defined: the elderly, women, patients with moderate renal impairment and structural disease and as I said modest efficacy in atrial fibrillation of somewhat longer duration.

As we saw yesterday, there is precious little information in ethnic minorities, a gap that the company recognizes and wishes to pursue in its post-marketing commitment.

The risks of tedisamil are relatively well circumscribed, I believe and consist principally of its risk of producing torsade in doses that exceed the recommended doses in particular. You've seen a point estimate and a confidence interval for the observations of torsade, both in men, as well as in women and as I pointed out in my opening remarks, we're particularly concerned in making these definitions in women as they are particularly susceptible to this adverse

event. And bradycardia and hypotension, a few cases, perhaps not more cases of hypotension than the placebo group, but still a cause of concern. But what I'd like to emphasize here is that -- and as has been stated several times previously, there are generic risks to conversion of atrial fibrillation to sinus rhythm. That is part of the price of doing business in atrial fibrillation. One of them happens to be thromboembolic events, especially the chances for causing a stroke in patients who are not properly anticoagulated. We don't have any evidence within this data set that tedisamil has a unique disadvantage in that regard.

So I would conclude that we have described a relatively favorable benefit-risk ratio with rapid and durable conversion of clear dose response, and a relatively low risk of torsade at the recommended doses. But we have the same problem today that we had yesterday which is that we have a drug that's

been demonstrated to be effective and for common adverse events, relatively well described safety profile, but we don't have a good description of adverse events that occur infrequently because we can't within the circumscribed database that we have of less than 1000 patients.

So two things, I think, are extraordinarily important and you've seen demonstrated. First, we propose a risk minimization plan that will give very precise prescribing information to physicians. I think this is extraordinarily important because as far as we can tell, the only way to over expose patients to this drug is by misadministration, either by giving it to patients who have severe renal impairment which is a population that should not receive the conventional doses that we described and excluded from this data set or by misadministration by a treatment mistake. And so we've tried, as best we could, and we're

9794f29f-afdd-43a9-98b8-c39d54484326

open to more suggestions about how best to optimize the dose administration to avoid misadministration.

And then finally, and I think very important in this era of scrutiny of drugs that are already approved, we believe that it is extraordinarily important to continue to observe the adverse events that occur with this drug over the longer term in a large data set. And we don't pretend to know all the answers to this. I heard some very good suggestions from Dr. Hiatt yesterday with regard to how one might construct these programs and I believe that the communication that we'd like to have with the Committee today should include some ideas about how this might be done because it's obviously extraordinarily important for drugs like this to have the potential to cause adverse events that may be infrequent, but are frequently catastrophic.

Thank you for the attention of the

Committee. I'm going to ask Dr. Raczkowski if he would please come back up to the podium so we can begin questions from the Committee when you're ready.

DR. RACZKOWSKI: Well, thank you for your attention and we'll be pleased to answer any clarifying questions that you may have.

CHAIR HIATT: I think the request is to take a break. It's in the agenda. So maybe give us 10 or 15 minutes and we'll reconvene for questions.

(Off the record.)

CHAIR HIATT: I think we're going to now turn to questions from the Committee. Thank you, everyone. Just to introduce this part, and during the break, I actually approached Dr. Straub and asked that, similar to yesterday's request, that we could look at a more kind of tabular summary of some of the key safety and efficacy parts of the development program. And so they're working

on this.

The list would be to primarily focus on 24 hours or time of discharge between drug and placebo, accumulating all doses and looking at kind of key major clinical endpoints like, death, MI, stroke, and there's also a nice couple of tables of thromboembolic events that we should also summarize and then some of the electrophysiological outcomes -- VT, torsade, bradycardia and hypotension.

So the idea that we could maybe look on a slide or two, a tabulate or summary, and that's all from the IV studies. I know Dr. Harrington might be requesting some information from the oral dosing studies.

And the other thing that we mentioned -- just to let you know what might be going on, Evan -- we can review this is an hour or so -- is looking at some of the key efficacy endpoints at 24 hours, once again recognizing that things happen after the formal treatment window of 2-1/2 hours, but

that would include the number of subjects who required d/c carcioversion or took prohibitive medications -- that's Table 44; and the number of subjects in sinus rhythm at 2-1/2 hours and 24 hours, by group, so that we could maybe just summarize that for our overall way to balance safety and efficacy here in a little bit.

So I just wanted to introduce that before we go into more focused questions. And the other comment -- I wanted just to clarify this. I think it's obvious, but for the record, you all didn't acquire any symptomatic information on these patients in terms of their symptoms of atrial fibrillation?

DR. RACZKOWKSI: That's correct. Patients were required to be symptomatic at the time of entry into the study, but we did not systematically evaluate their symptoms afterwards.

CHAIR HIATT: But perhaps based on what we know, the cumulative evidence over the