

presented earlier, the two samples the pharmacy compounded, were obtained from two of the larger suppliers, as far as we know and two of the ones that we believe to be the most reputable, again, I don't know how you make those determinations, but these were not -- both of these places advertise on the Internet. Both of them, as far as we know, distribute a fairly large number of prescriptions annually of fampridine.

And those prescriptions were quite variable in their quality, as you saw.

DR. LIEBMAN: I don't mean to be argumentative. Just because they make a lot of them doesn't necessarily mean that they are skilled at what they do. It only means they make a lot of them.

DR. COHEN: No argument, but then I think one has to face the question of on what basis does the population at large and physicians at large make the determination of what is a high quality producer and what is not. I think, in fact, what happens is people are all -- as long as compounding is allowed, people will obtain the drug from whoever is supplying it and I don't see a good way of regulating that without, in fact, regulating the development of the drug.

DR. BEVER: I will repeat my comment in the microphone that I gave before. And that is we did just

give a list of pharmacies to patients and tell them to find out what the cost was. My problem is that a clinician is -- is that it is not easy to get data on compounding pharmacies that would allow me to distinguish a good one from a bad one. We had picked what we thought were fairly reasonable ones through patients to get drug that was analyzed by Elan and that didn't help us.

DR. PECK: You are going to have to be careful about listening to me because I may generate some thoughts by you that you will disagree with.

Data was prepared by your firm or Elan, which talked about the poor quality as was judged by weight variation and so forth from the two sources of this compounded product. These information were given to us and then there were some assay -- limited assay data presented.

You will probably say we don't have to do this, but you have not presented anything that would indicate the superiority of either the capsule or the tablet formulation showing that there is diluent interactions, migration into the capsule shell, which is not uncommon. Many drugs do this. While you can say, however, that the Agency will be given this particular information, but we as a committee have to sit here without this information and make some decision, which is a little bit in favor of

you in terms of no compounders can do their work.

I am not sure whether I am clear as to what you were saying out of your letter.

DR. COHEN: If you could clarify the question that you want me to answer in that?

DR. PECK: Do you have data that demonstrates that your products are superior?

DR. COHEN: I believe that Elan does, based on our investigation of Elan's portfolio and Elan's data.

DR. PECK: But that would be available probably only to the Agency?

DR. COHEN: Sharon? Yes.

DR. KATZ: Yes, I think one of the great advantages of requiring that studies be done under an IND is that there are strict standards, as you undoubtedly know, about the strength and the identity and the purity of products that are permitted to be given to people under the IND. Without speaking specifically about any product, I think in this context, one of the great advantages is just that, that we have seen that there is considerable variability in the compounded products and we have standards that sponsors are always required to meet for the composition of products under INDs, just as a generic statement.

DR. JUHL: We have been told that the new

product meets these standards and exceeds that of the compounded ones. But we are asked to trust that without data, I guess, is --

DR. KATZ: Well, as Dr. Behrman said, I mean, part of this -- to the extent that certain things are not -- are confidential under the IND and can't be discussed in public without the permission of the sponsor, that is a large part of what we do.

As she said, you will have to consider whether or not you trust us to do our job so that we would permit a product that meets our standards under the IND. Again, it is what we do. We do it everyday and we think we do it well and we have standards that are sort of public and folks have to meet them if they want to give a drug out under an IND.

DR. JUHL: Is that satisfactory, Garnet?

DR. PECK: Yes. I wanted a clarification of this particular situation and the judgment and the data that is available. The IND situation is very important to the development of new drug products and there are certain things that are in there that must be retained in confidentiality. But I don't like mixing economics with this confidentiality. That part -- I am trying to separate that to evolve good products.

DR. BEHRMAN: We are really not -- we, FDA, are

not thinking about the economics. We have one decision to make with your help, which is whether or not this product should be on the compounding list.

The second decision is the IND development and actually they are in a way unrelated. The Elan product doesn't have to be superior. As Dr. Katz said, it has to meet our standards. We wouldn't be particularly interested in the comparison, in fact. But we are not particularly worried about any company's economics right now. We are worried about the safety of the patients who will get these drugs.

MS. AXELRAD: I was just going to comment that people that are here from the Review Division weren't here this morning during the discussion, but it was sort of my understanding that we discussed the possibility of whether something should be put on the compounding list or not put on the compounding list, with the understanding that if it was going to be used, it would be done under an IND and we didn't have any information on any formulation of it at that time. We had some generalized safety information from the literature, but I think, certainly, the committee's vote with regard to DNCB was that it should not go on the list and that you would rely on the agency to make sure that if it was made available under an IND, that it was -- that an

appropriate quality product was made available and we sort of indicated that we would be carefully considering the chemistry, the impurities and other issues associated with that if we were to allow it under an IND.

So, I think the discussion that we had this morning sort of relates to what we are talking about now and if we are talking about the same situation and we would be looking at the product, the division would be looking at the product very closely under an IND and under any kind of an open label trial.

DR. JUHL: I think the one thing that is different, at least in my mind, I am greatly appreciative of the company's offer to have an expanded access program under an IND where we can collect more information. My concern is your ability to deliver and the past experience made me real nervous because we have patients out there that I think are doing better on the drug than they would do without the drug.

There is no question they would do better with the manufactured product than with the not manufactured product. I want to be confident in your ability to do that and you are essentially putting the gun at the head of the patients and saying either do this or we pull the trigger. I think the committee is reacting to that difficult decision. I am not arguing with you. I

understand, but it is an uneasy one for the committee --

DR. COHEN: Well, it is an uneasy one to hear fed back that way because it certainly -- we certainly don't intend it to come off that way nor do we feel about it that way. You know, it is not a -- it is really holding a gun to our own heads if you really want to put it that way.

DR. JUHL: I am reacting to your tone and your forcefulness on the do this or we are out of here kind of thing.

DR. COHEN: Then I willingly stand down from the tone and -- but still want to emphasize the point that it is not a question of us -- of do this or else by any means. We would not be so bold as to attempt to come before this panel and come off that way. It is simply a question of what we are trying to do in good faith, which is to assess what can we do and under what circumstances can we do it because we have our own constraints back home in terms of what we are able to do.

In analyzing that, our best judgment in good faith is that we are able to -- we would be able to supply the drug in a large expanded access study and we want to do so and we are willing to do so, that in the event that compounded drug continues to be unavailable, we will not be able to pull it off. And it is not a

question of want to or not want to. We simply won't be able to pull it off.

If I didn't convey it that way, I apologize. That is what the reality is.

DR. JUHL: Yes. And I understand that and I appreciate you being forthcoming and not beating around the bush. Let me put it that way. But that is a decision we end up being -- you understand our --

DR. COHEN: I understand.

DR. RODRIGUEZ: I have concerns about some of the data that was presented and the concerns are not on the data per se, but on the implications of the data. When you have some things in which the actual sample is one-third of the dose and we have such a narrow type of safety, I just wonder what is going to happen in the meantime with this information because we are talking about safety and we are talking about there are a lot of people taking medication, who may cross the state line and go on some other compounding pharmacy and have been used to a 3.3 milligram and end up with the 9.2 milligrams for 8 milligram capsule.

Those things just worry the hell out of me as I sit over here thinking as a consumer to put it bluntly. So, I like the fact that you found that. We have lacked this information in many of the other products. We are

trusting the fact through the Agency that this was conducted in an unbiased way and then the information is even if we go ahead and say there should be no compounding, for example, there is going to be a lag in between. This information is, quote, unquote, your information and the question is what do you do with that information in the meantime because the people who use this medication are pretty much I would say involved in their destiny and if they were to find out that there were just differences in between the preparations, they will at least demand that that information be available to them.

Just a commentary.

DR. JUHL: Loyd, perhaps you could comment on the extrapability of those findings. I know there was one study that was published in your journal that showed maybe 10 percent, plus or minus, was about as good as you could expect under the best conditions for compounding. Here we have capsules with very small milligram amounts. What is reasonable to expect?

DR. ALLEN: There is no question those are outside. In fact, pharmacists that compound are required to meet the requirements of the USP for their products and clearly those are outside the limits. According to Phadema(?) 1997, the USP general chapter on compounding,

which up until now has been an informational chapter, now moves down into the enforceable area and that process is ongoing right now.

Compounded pharmacists must meet the requirements for the preparation of a product. If there is a monograph in the USPNF, it has to meet that. If not, well then it goes to the general guidelines of the general chapter. And we are looking at generally -- you know, most stability studies and things like that, plus or minus 10 percent of the target quantity of drugs. This would then -- if an individual pharmacist is not performing to that level of expertise, then that would fall into the enforcement agency, you know, the state boards, et cetera, in order to investigate that.

So, you know, clearly, that is outside the area of accepted practice, because plus or minus 10 percent is what is normally reasonable.

DR. JUHL: I wonder if I could ask Jane, does the MOU with the state boards include provisions that lead a board to investigate this kind of detail or maybe I could ask Carmen the same question.

Do you expect boards of pharmacy to go out and purchase samples, do the analysis and do a quality assurance in that fashion?

MS. AXELRAD: I would sort of have to defer to

Carmen about whether they would actually go out and purchase samples, but I would say, certainly, at least, we don't have an MOU in place or anything right now. Certainly, the way we are dealing with enforcement issues is if we became aware of a situation through one way or another of something that was really out of compliance with the USP chapter on pharmacy compounding, we would probably want to consult with the state in which the problem was identified and between us decide what kind of an appropriate enforcement action would be taken.

But I don't think we are doing a lot of inspecting right now of compounding pharmacies. Because of the uncertainty, we don't have any regulations in place and we are in the process of implementing it. But I don't think that we, ourselves, are doing a lot.

DR. JUHL: Would this information that has just been presented be fed back to the appropriate state board or to the pharmacy that produced these products in an effort to improve?

MS. AXELRAD: It could be if we had specifics on -- we would have to have specifics of what pharmacy -- specific information about it.

DR. SELLERS: Loyd, this is directed more towards you, but if compounding pharmacists are supposed to be meeting USP specs, how do they know if they are

meeting those specs?

DR. ALLEN: Basically, there is no requirements that they have their products tested. What it is based on is whenever you get a certificate of analysis, where the product is 98, 99 percent pure as far as active is concerned, and then you have a formulation -- let's say you are preparing 100 capsules. Okay? 25 milligrams each. Well, then you would weigh out 2.5 grams plus your excipients, prepare the 100 capsules at one time, equal distribution, check the whites, and that basically is all that is required at this point.

I always recommend that occasionally -- of course, you can't do it on compounded prescriptions that you get just occasionally because it wouldn't be financially feasible, but if a pharmacist is doing a product routinely, you know, every week, every couple of weeks, that they periodically take samples and send them all to a contract lab for analysis, of which many of them do. Many of your better ones do, like Dave was referring to awhile ago.

MR. TRISSEL: Apart from those issues, really a pivotal thing is -- I think we can all agree that to get a GMP manufactured product with GMP bulk, GMP manufacturing process in a suitable plant, a consistent product in the hands of all the patients who need it,

would be a desirable situation.

The question only is really can that be delivered in terms of several thousand, maybe 5,000, maybe even more, patients. It would seem reasonable to give that a try and see if the company can deliver on their promise and we have a promise from you, right, that you will --

DR. COHEN: You have a commitment from us that we will do that.

MR. TRISSEL: -- for all patients whose physicians believed this would be of benefit.

DR. BEHRMAN: The answer to that is -- it would be impossible for any sponsor to address that because we would want to discuss the contents or negotiate the contents of the program with them. As Dr. Woodcock mentioned yesterday, second to the safety of the patients is the safety of the development program. If we believe that the expanded access program is going to make it impossible to develop the drug, we will put certain limits on that program. It is important to remember that there is not a right to access to drug in this country. That is nowhere in the law. It is done because -- it is done for a variety of reasons, but only when appropriate.

So, that means that it is always appropriate in the programs where the sky is the limit. I mean, when

people think about expanded access, they think about some of the very large AIDS programs that we described for you yesterday, where, for example, 35,000 patients received 3TC. But that is not necessarily what is going to happen.

We may not determine that it is appropriate for every physician, who wants to get a patient on this program to do that. We may decide that we don't know enough about the safety. We don't have sufficient efficacy data or there is not sufficient drug supply.

So, again, you would have to trust us to negotiate a fair and appropriate program with the sponsor.

DR. COHEN: I think I will only add that in terms of drug supply, from our point of view, we -- I will just repeat that we are capable, willing, able to supply certainly substantially more than the 5,000 number that you mentioned. If it were necessary and if it were agreeable and appropriate under the regs and in our negotiations and discussions with CDER.

DR. BEHRMAN: Because remember that any experimental drug carries with it -- well, any drug carries with it a risk, but particularly experimental drugs. We in that sense sort of try to stage the expanded access program so that the smaller ones are for

the patients that have absolutely no options and clearly want to and are able and, if justified, tolerate the risk, as opposed to when we are much more confident that the drug, in fact, works and we are simply waiting for either the NDA to come to us or for us to finish the NDA, when a somewhat looser program is more appropriate.

MR. GRADY: I am Tim Grady. I am with the U.S. Pharmacopeia that has been mentioned here.

I missed the first 10, 15 minutes, so you may have covered this, in which case I apologize for the intrusion. The high variability is very suggestive of a vapor pressure problem. This was reported, for example, by Professor Ralph Shangra(?), the late, great Ralph Shangra, on nitroglycerine. So, the question I have with the compounded preparations, were they labeled to be refrigerated? Were they delivered with a beyond use state? Or has anybody formulating this material as a salt? I mean, you have got a lot of electrons coming off of the neferadine(?) nitrogen and you have got amino group -- by the way, your amino purity is very easily -- you can bubble air into water with some of those molecules and make a nitroso compound.

So, very hot electron situation. So, the question is anybody making a salt out of these? So, I don't know that you can characterize the compounding

situation for something with a high vapor pressure and I don't think the pharmacists should be beat up for the variability. It may well shop within the 10 percent that Dr. Allen is talking about, but a couple of warm days will take care of that.

MS. AXELRAD: I just wanted to clarify my earlier remarks about this and that is that the -- I was reminded that the statutory requirements that you comply with the compounding chapter and any USP monographs, if one exists, goes to the bulk drug substance. It does not go to the finished dosage form. So, there is nothing in the compounding law that actually specifically says that the finished dosage form, the actual compounded product has to comply with the USP standards.

DR. LIEBMAN: Loyd, I thought when we wrote monographs for compounded products, we said the finished product has to be plus or minus. Jim, do I remember correctly, on compounded drugs? Jim, are you still here?

DR. JUHL: We can get clarification on that point because it is written down somewhere.

Let me ask one more question and then we will let you go.

Your distribution system, as you would see it, would be a centralized one or would you make use of pharmacists, who already have relationships with these

patients, and attempt to take advantage of that?

DR. COHEN: We actually have been in discussions with a couple of contract research organizations, who -- one of whom in particular has specialized in managing and directing other expanded studies, particularly for some HIV compounds and some cancer compounds in the past, studies that have involved in some cases tens of thousands of patients.

So, our intent would be to contract with those organizations and follow their best recommendations as to how this would be distributed effectively. So, I cannot comment knowledgeably, personally, to you now about that, but I will tell you that we are --

DR. JUHL: You are not considering using the pharmacists that already have those patients?

DR. COHEN: Again, I don't know the answer to that question because this is not an area that I am expert in. This is something that we will rely on the contract research organization to advise on and it may well be. We haven't had that specific conversation with them yet, but if they were to say, you know, an effective way to do this would be through these pharmacies that are already accessing these patients, that would be -- obviously, we would do that.

DR. BEHRMAN: It may be worth noting that that

would be very atypical, because you have to have a physician to actually write the prescription or prescribe it. The interaction is between the physician and either the company or whoever is acting on their behalf.

DR. JUHL: I understand but, again, we are atypical because there are already patients on these drugs and how you are going to find them is the question.

Other questions?

[There was no response.]

We are running a bit behind schedule and I thank you. We will probably have some additional discussions after break, but I think we will take our break now and get to our next speakers on the diaminopyridine right after break.

Let's be prompt and be back in the room at five minutes after.

[Brief recess.]

DR. JUHL: Okay. We will resume.

Agenda Item: 3,4-diaminopyridine

We will now move to 3,4-diaminopyridine. We will then have an open public hearing where both compounds will be discussed and then the committee will deliberate on both compounds following that.

First, we have Dr. Donald Sanders from Duke University, who will talk to us on his experience of 3,4-

diaminopyridine.

DR. SANDERS: Thank you.

I am going to be talking about the use of 3,4-diaminopyridine in neuromuscular diseases, predominantly Lambert-Eaton Myasthenic Syndrome. For the last 11 years, I have held an IND for 3,4-DAP, primarily to use it in Lambert-Eaton Syndrome. So, I am going to start with an introduction to that condition.

This is a very rare neuromuscular disease, affects probably fewer than a thousand, 1,500 people in the United States at any one time. The exact numbers are hard to come by because it is quite frequently undiagnosed or misdiagnosed.

It is a condition that affects muscle strength, begins typically with weakness of the legs, progresses to the arms. The clinical findings that lead us to the diagnosis are listed here. We find weakness in the hip and shoulder muscles. Tendon reflexes are reduced. Most patients have some evidence of autonomic dysfunction, particularly a dry mouth and occasionally they have weakness of the eyes or muscles that control their chewing, swallowing or talking.

It results from an autoimmune attack against the voltage gated(?) calcium channels on the presynaptic motor nerve terminal. Actually, the condition affects

many nerve connections in the peripheral nervous system, but the one that produces the weakness is diagrammed here. This is a neuromuscular junction, presynaptic nerve here, postsynaptic muscle membrane here. On the tips of the folded postsynaptic membrane are located the receptors, which receive the acetylcholine that is released from the nerve terminal.

In the Lambert-Eaton Myasthenic Syndrome, there are antibodies directed against the presynaptic voltage gated calcium channel. These antibodies block the release of the acetylcholine and that produces the weakness.

These antibodies act by cross-linking the voltage-gated calcium channel, which leads to their down regulation, reduction in numbers and there is also some evidence that the IgG, the antibodies, actually block calcium influx through the calcium channels.

About 50 percent of patients with Lambert-Eaton Syndrome have it as a paraneoplastic syndrome; that is, it results from an underlying cancer, usually a small cell lung cancer.

These are cancers that predominantly, if not exclusively affect smokers and, thus, if a patient with Lambert-Eaton Syndrome is over age 50 and has a history of smoking, they almost undoubtedly have a small cell

cancer.

In these patients with cancer, presumably these cancer cells, which are rich in voltage gated calcium channels induce antibodies that cross react with the nerve terminal voltage gated calcium channels. In the 50 percent who do not have an underlying cancer, then, presumably, this disease is a part of a more general autoimmune state.

These are the ways that we go about treating Lambert-Eaton Syndrome once it is diagnosed. The first thing we do is to look for an underlying cancer and treat it if it is found. Many patients will -- if they are successfully treated for cancer, will have improvement if not resolution of their weakness and, thus, sometimes don't need any further treatment.

However, the majority of patients do need treatment. This is a disease that produces variable degrees of debility. Most patients have moderate to moderately severe dysfunction, which means they are able to carry out their activities of daily living, but not their normal activities. Rarely, the disease produces such severe weakness as to be life threatening.

We begin treatment by seeing if they will respond a cholinesterase inhibitor. Mestinon is the one that we use most frequently. It doesn't usually do very

much, but occasionally some patients will get benefit, particularly in some of their autonomic symptoms.

Based on our experience and the experience of others throughout this country and throughout the world, we considered 3,4-diaminopyridine to be the next treatment of choice, if it is available. If it is not available, then guanidine, which is an agent that has been used for many years to treat Lambert-Eaton Syndrome is sometimes used. It has a very high toxicity profile, however, and most people who have used it, including the patients who have used it, would prefer not to.

We do consider the use of various forms of immunosuppression in these patients, depending upon the severity of their disease and how well they respond to 3,4-diaminopyridine. Things that have been used with variable success include high doses of steroids, such as prednisone, other immunosuppressants, such as azathioprine(?) or cyclosporin, plasma exchange or high doses of IV Ig also can produce significant, though temporary, improvement.

In these patients, even if we don't find a cancer initially, we frequently and periodically reassess for the presence of cancer, which may not have been detected initially.

3,4-diaminopyridine has been used in the

treatment of Lambert-Eaton Syndrome now for -- I can't see the date -- is that 1984? Okay. That was the first report of its use in Sweden. The reports were so enthusiastic that whenever or wherever it could be obtained, it rapidly became the treatment of choice everywhere in the world, except in this country, where it has not been available, other than on protocol.

3,4-DAP, like 4-AP, blocks the voltage gate, voltage dependent fast potassium channels in their closed state, which prolongs the falling phase of action potentials throughout the nervous system, which then enhances the calcium entry into the nerve terminals, which then enhances transmitter release.

These are some slides made from studies we did more than 20 years ago on 4-AP in action potentials from normal and myasthenic patient muscles, just to show what it does to an action potential. This is a normal muscle action potential and this is its prolonged form after having been exposed a low concentration of 4-AP. This is what 4-AP does to Lambert-Eaton Myasthenic Syndrome neuromuscular junctions. We infer that 3,4-DAP, which has a very similar mechanism, does the same thing.

Here on the top we see in plate potentials recorded from the post-synaptic muscle, initially in a controlled solution and then at various times after 4-AP

is introduced into the solution, showing the enhancement of the amplitude. Here at the bottom is just a longer term diagram of the same thing. The amplitude increases and ultimately becomes normal and effective in producing muscle activation.

This is a slide from that initial report from Hoken(?) Lund(?) and his co-workers from Lund, Sweden, showing what happens to the muscle response that is elicited by a nerve stimulation in a patient with Lambert-Eaton Syndrome, after administration of initially -- this is diaminopyridine by itself and this is diaminopyridine with an acetylcholinesterase inhibitor at the same time, showing that the action of these two works -- the actions of these two are synergistic and much more than either alone.

There has been one controlled study of DAP published to date. This is a study by Katy McEvoy and Tony Windebank and others from Mayo Clinic, which was published in the late eighties. This was a small series of patients, but the benefit both in terms of their function, the electromyographic muscle recordings and autonomic symptom improvement in patients receiving it for Lambert-Eaton Myasthenic Syndrome.

We have been using it since 1988 for this purpose and to date have treated 53 patients with LEMS.

We have had a couple of blinded studies, the most recent of which has just been completed under sponsorship of the orphan products program and the results of which, although we know what they are, I haven't got the data to actually show you the numbers. But this is a summary of the clinical response in these 53 LEMS patients that we have treated so far.

Forty-five percent had a marked improvement. By that, we mean they achieved relatively normal functions of activities of their daily living. Thirty-four percent had moderate improvement, which means a significant improvement in their lifestyle and a smaller percent had either minimal improvement that was not enough to justify continuing its administration and a very small number had no response to DAP at all.

The obvious conclusion here is that in this disease for which there is no other really good treatment, the overwhelming majority gets significant benefit from DAP.

This is a slide for a press release -- you can use this if you like -- showing a patient with Lambert-Eaton Syndrome before and after she received a single dose of 15 milligrams. Here she could not lift her arms over her head and here she was brightly smiling and reaching for the sky. She was delighted when I told her

I was coming here and I was going to show her picture. She is one of our enthusiastic customers.

These are some measurements from the most recent study that we have completed. We did a study that involved the treatment of 26 Lambert-Eaton Syndrome patients. It took us five years to accumulate these, but these are the data using as a measurement of efficacy a quantitative function score, which involves timed measurements of the function of various muscle groups in the body that is then summated.

We see that the scores in the patients who receive placebos -- this is the change in their QMG score from a baseline -- is really no different from the baseline value here; whereas, after the administration of 20 milligrams DAP three times a day for five to six days, their QMG scores had significantly fallen.

This just shows the change in QMG score amongst these patients, comparing those who had received placebo, virtually all of whom had very little or no improvement in their QMG score versus the patients who had received diaminopyridine, showing that there was a variable change in this score, but virtually all patients had significant improvement.

Similar observations on the muscle measurements that are used to quantitate the severity in this

condition, the compound muscle action potential, which is the size of the electrical response you elicit from a given muscle when you stimulate its nerve. Here on the left, the placebo group showed no change from their baseline values after five to six days; whereas, the amplitude of this muscle response was significantly higher in the patients who had received blinded diaminopyridine.

This study involved an initial blinded phase and a subsequent open label phase during which we optimized the dose to determine the best dose response in individual patients. These are the ultimate doses that we determined to be optimal in the 24 patients, who ended up taking open label drug.

The dose was sometimes as low as 20 to 30 milligrams a day, but occasional patients took doses up to 80 or even a hundred milligrams a day to achieve their optimal benefits. So, there is a variable dose requirement in this condition among patients.

After determining the optimal dose in patients, we then added Mestinon to it to see if that would make them better or if not, would allow us to reduce the dose of DAP to a lower level in order to avoid side effects.

Patients require anywhere from 5 to 25 milligrams per dose in order to achieve their maximum

benefit. It is administered every three to four hours during waking hours and in almost all patients, the addition of pyridostigmine, Mestinon, at a dose of 30 to 60 milligrams, three or four times a day, significantly prolongs the duration of action of the medication and/or increases its maximum response.

The side effects are usually trivial. Perioral and digital paresthesias are reported by most patients, who take doses higher than 10 milligrams, these paresthesias occur usually 10, 15 minutes after the patients take a dose and are rarely unpleasant. In fact, I have some patients who tell me that it is actually a nice little buzz.

If the dose is taken late in the day, it has produced insomnia in some patients. Seizures are a problem if high doses are used. When it was initially introduced or described in Europe, doses of a hundred milligrams a day were the recommended standard and that is doses that we used initially in our protocol as well and the Mayo Clinic protocol used that dose as well.

On that dose, there have now been to my knowledge three patients who have had seizures. One of our patients did. We don't use those doses now, primarily because we have found with experience that by using cholinesterase inhibitors along with DAP, we don't

need to use such high doses to get the optimal benefit. But it is necessary to titrate the dose in each patient individually in order to determine that.

Since DAP and cholinesterase inhibitors do have synergistic actions, the DAP can enhance cholinergic symptoms in these patients, cramping, diarrhea, that sort of thing, nothing really of major concern.

I am sorry you can't see this slide. I can't either. But it is just to remind me of some of the symptoms that we queried the patients about in this blinded study that we performed and it really showed that there was no -- the only symptoms that were significantly more frequent in patients receiving drug compared with placebo were related to the paresthesias that they had.

In conclusion or at least in summary of our experience, we found that 85 percent of patients with Lambert-Eaton Syndrome obtained significant clinical benefit from DAP with no significant side effects at the usual clinical doses. The benefit is complemented by Mestinon and at least at the present time it is available only on protocol or for compassionate use.

We initially obtained diaminopyridine as a purified commercial product from a commercial chemical company, but about five to six years ago, Jacobus Pharmaceutical took it on as an orphan product and has

been providing it for us at no cost since then. They have recently developed a pill formulation. Initially, we obtained it as a purified powder. Our pharmacy mixed it up in capsules for us, but now we are getting it in pill form. It does have to be kept refrigerated in order to maintain its integrity.

We keep it frozen in our laboratory and send it out in refrigerated containers to patients who are receiving it. This works as long as Jacobus continues to provide it for us and we can continue to afford to pay the postage for the patients. We haven't yet figured out a way in which the patients themselves can pay for this.

The way we begin it usually is to have the patients taking 10 milligrams three times a day for two weeks and observe the response. We then increase the dose by 5 milligram increments until we have determined its maximum effectiveness based on primarily the patient's symptoms, not to exceed 80 milligrams a day.

After we have done this, we add Mestison in graded doses to reassess the maximum effective dose and it is necessary to periodically reassess the optimum dose in these patients because the disease changes over time. We have had some patients who have had spontaneous improvement and don't need as high doses as they previously did. And we would never know that unless we

had this periodic reassessment. So, that is built into our protocol.

There has been some concern about cardiac toxicity, theoretical concern, based primarily, I think, on what it does in experimental animals at high doses. To my knowledge, there has not been any report in the literature of any such effects on patients and we have not had any. But to examine the effect on the heart rhythm in the study that we did, we looked at the corrected QT interval, the QT interval and the corrected QT interval and EKGs in the patients on DAP and on placebo and this is just to show that if anything the patients who receive blinded DAP had less of a change in their corrected QT interval than the patients who were receiving placebo. But there is no difference and we don't feel that there is any significant cardiac toxicity at the doses that we are using or likely to use.

What has been the response in our experience to the other treatments? A very confusing graph, I think. Probably this table, if you can see that, is more informative. We did a retrospective study or evaluation to see how well other forms of therapy had benefited the patients that we have seen.

We compared those with the benefit from diaminopyridine and I think if you just follow the top

two lines over here, you will see that percentagewise none of the other treatments even comes close to the benefit that patients obtain from diaminopyridine.

So, in conclusion, in treating patients with Lambert-Eaton Syndrome, we always go after any underlying cancer because occasionally treating that can produce marked, sustained benefit. Pyridostigmine, Mestinon, by itself is usually ineffective. Diaminopyridine is usually beneficial and even more so when used with pyridostigmine. Plasma exchange and high dose immune globulin frequently give marked, though, temporary improvement in these patients.

I don't consider these forms of therapy to be viable, long term therapies in patients because of logistics and expense, but, occasionally, they are necessary. Other forms of immunosuppression produce variable degrees of benefit in some patients, but rarely gives marked benefit and in my experience has never given patients as much benefit as they get from diaminopyridine.

I want to take just a couple of minutes to present a couple of cases to exemplify how we use it and how it has worked. This patient had the autoimmune form, non-cancerous form of Lambert-Eaton Syndrome, which began when she was 39 with proximal leg weakness, which

progressed over several months to involve her upper extremity muscles. She also had some mild weakness of her eyes and bulbar muscles.

The diagnosis was made by electrophysiologic testing and no malignancy was found. She was initially begun on Mestinson, which produced some mild improvement and then she was begun on asathioprine, an immunosuppressant. Didn't really do very much. She had three treatments with plasma exchange, each of which produced dramatic but transient improvement.

She also received five treatments with IV Ig, which, again, produced some transient improvement. Steroids was given in high doses, which produced what was referred to as good improvement, but she developed a vascular femoral head necrosis, a recognized complication of prolonged steroid administration. She joined our protocol early on. She achieved dramatic sustained improvement with diaminopyridine. Her optimal dose was 10 milligrams every three hours with 120 milligrams of Mestinson every three hours.

She has now been on DAP for, I think, six or seven years and you would be hard put to get it away from her.

This is a patient who has the paraneoplastic form of Lambert-Eaton Syndrome. He was a smoker. At age

39, he began to have trouble with skiing and progressive fatigue, proximal muscle weakness over the ensuing months and the diagnosis was made seven months after onset. His cancer was not found on the initial screening, despite the fact that very vigorous screening was done. He was treated with Mestinon with no benefit. Prednisone produced slight benefit. Guanidine produced increased endurance and strength, but he had lots of side effects from it that were unpleasant and he joined our protocol in 1992.

He had a dramatic improvement with 20 milligrams, three times a day. He was able to walk. He actually went back to work. Unfortunately, about a year and a half later, he developed brain metastases, which were the first manifestations of his lung cancer. Seizures came along with that. So, we had to stop his DAP and when we stopped his DAP, he became bedridden. He died several months later of the results of his cancer, but after his death, his wife wrote me a very poignant letter in which she said he wanted me to tell you this, that you had given him two years of useful strength because of the DAP.

Thank you.

DR. JUHL: Thank you, Dr. Sanders.

Questions? Dr. Gilman.

DR. GILMAN: When I looked through this material and then hearing the commentary this morning, I was rather unimpressed with the beneficial effects in multiple sclerosis of this agent, of 4-AP, but very impressed with the benefits of DAP in Lambert-Eaton Syndrome. I also called colleagues at the Mayo Clinic, the people who had done the initial trial in 1989 with Lambert-Eaton Syndrome.

They have about 30 patients ongoing that they are treating and I would say their e-mail message reflected your experience, that it is very effective and that it is very safe. So, I didn't get any quantitative statements from these people and I wanted to ask Dr. Sanders. So, you go up to a maximum of 80 milligrams per day. What is the prevalence of seizures on that dose?

DR. SANDERS: I don't know of anyone who has had seizures on that dose, other than patients, such as the one that I just presented, who had brain metastases. He had demonstrated brain disease, which is probably the cause of his seizures.

DR. GILMAN: Do you get seizures with any lower dose?

DR. SANDERS: I have never heard of anyone getting seizures at a lower dose, other than those circumstances.

DR. GILMAN: Do you monitor the blood levels in these patients?

DR. SANDERS: No, we don't. We have not found that the dosage that we use produced blood levels that are detectable using the techniques that we have had available to us.

DR. GILMAN: Do you have any evidence suggesting that different compounding pharmacies produce different concentrations or highly variable responses in your patients?

DR. SANDERS: We have only obtained the DAP from the sources that I indicated. I wouldn't have any way of knowing whether a compounding pharmacy would be able to produce the drug at the concentrations and with the reliability that we have been achieving it.

DR. MC BURNEY: Dr. Sanders, as I understand, you have had no difficulty in obtaining the drug when a patient needed it?

DR. SANDERS: No difficulty in obtaining the drug -- well, it is a complicated process. It is a three-way -- you know, it is a three ring circus. We get the drug from Jacobus Pharmaceutical. We store it. We send it out to the patients when they need it. They resupply us. I wouldn't say we have no difficulty, but we have had no patients who have failed to receive it.

DR. MC BURNEY: So, there has been availability.

DR. SANDERS: There is availability but there are problems with the availability, as I mentioned before.

DR. RODRIGUEZ: You mentioned that things have -- the medication has to be kept frozen or refrigerated and the question that I have is realizing the realities of human beings, what is the stability, for example, at room temperature? Would it last 24 hours, 6 hours, 8 hours, 10 hours? You are giving it three times a day and that means that people will have to have access to a refrigerator three times a day. I was just sitting over here thinking as somebody who takes medications regularly, what is the -- would six hours be -- still give you the same amount of strength or potency that you wanted?

DR. SANDERS: I am going to defer any questions like that to someone who knows a lot more about that issue than I do. We keep it frozen in the laboratory until we dispense it out of just precaution. Whether it makes that much difference that it is refrigerated or not, I don't know. We haven't done the sort of studies necessary to demonstrate that.

Considering the inherent unreliability of

patients in taking medications the way they are prescribed, I think that if it were really a problem, we would have heard about it from some of our patients. I am sure they leave it unrefrigerated from time to time.

MR. TRISSEL: If I understood you correctly, your initial cadre of patients were treated with pharmacy compounded capsules from raw material.

DR. SANDERS: That is correct. Through our research pharmacy at Duke University.

MR. TRISSEL: And there were successes then, I gather, using that material to lead you to believe that this was a successful product?

DR. SANDERS: Yes.

MR. TRISSEL: I notice that the distribution of patients enrolled on trials is non-uniform in the United States to say the least. That looks like North Carolina and Minnesota have the lion's share of the patients and I can't believe that the patient distribution is really like this.

DR. SANDERS: The patient does go where the drug is, sir. Our patients come from all over the United States.

MR. TRISSEL: They do?

DR. SANDERS: Yes. We turn them into Blue Devils when they get there.

DR. JUHL: This is location of the physician, not necessarily where the patients are from.

DR. SANDERS: Exactly.

I didn't mention the potential value of this medication in other neuromuscular diseases, but we and others have also used it in occasional patients with congenital myasthenia gravis, which is a very rare group of conditions for which there are few good therapies. We have had good results in some of these patients. So, that is another indication for this medication.

DR. KATZ: I just want to reiterate one caveat about the warrant of safety at lower doses with this or any drug, but here specifically. Even if it were the case that we had complete follow-up or complete knowledge of patients experiences at doses lower than a hundred -- and maybe we do have complete follow-up, I don't know -- the number of people who have been exposed to any dose, let alone a dose lower than a hundred, is pretty small, I think. I don't know what the totals are, but I think in the Mayo Clinic -- well, we have the numbers here. Okay. So, it is not that much.

So, even if you had not seen any seizures if they had a lower dose, the warrant that -- the risk that you can cap with that experience is fairly high. So, it is possible it could -- we know the drug or at least we

believe the drug is capable as a molecule of causing seizures. It is certainly -- given the variability in the population, it is possible that it could cause seizures at a lower dose of -- and you can figure out what percent and you still wouldn't have seen any in this very small cohort of patients who have been exposed. So, it is just something to consider.

DR. SANDERS: We have been in contact with the groups around the world, who have had extensive experience with this. Dr. Lund now has treated patients for -- well, since before he published his first report in 1984 and the Mayo group, as you mentioned, have treated about 30 patients. So, probably the world's -- these three groups probably represent most of the world's experience with it and none of these folks, to my knowledge, have seen seizures at a dose less than a hundred milligrams a day.

The availability or entry of DAP into the central nervous system is much lower than 4-AP, as you know, and that is its main advantage in treating patients with peripheral nervous system diseases.

DR. JUHL: Thank you very much, Dr. Sanders.

Our next speaker is Dr. Jacobus, who is president of Jacobus Pharmaceuticals.

DR. JACOBUS: Mr. Chairman, the slide

projectionist is Laura Jacobus. I am Dave Jacobus and I do work in the Jacobus Pharmaceutical Company. And we are a small company that actually makes the active ingredient and then makes the dosage form and then does the appropriate registration and distribution and so on.

We synthesize the active ingredient, 3,4-diaminopyridine, in addition to making the dosage form. Now, this first slide is the slide to which I think Dr. Sanders responded. There is a huge concentration of patients there. The Mayo Clinic, Katy McEvoy, Tony Windebank, and this is Constance Bowe, B-o-w-e, a pediatric neurologist, and she has patients from this part of the country all the way over to here.

She has been a very active investigator and has done preclinical work as well. Now, for this committee, this committee should understand how these patients got on this chart because these don't represent pharmacy dispensing patients because we don't have a record of them. These are the patients in our roles and these are all physician-sponsored, investigational, new drug applications.

For the major centers, such as Don Sanders center, he has his own IND and the study goes along and it is well-established. But what happens when an investigator from an isolated state has an emergency, has

a patient in whom the diagnosis is made. They call us or we get a call relatively soon and we send -- for those of you who are not in either the Agency or maybe in industry, it is nice to hear how this system works.

We send a package of information to them so they can get an investigator-sponsored IND. We help them with the forms, but they have to write the letter. They send it to the Division of Neuropharm. The consumer safety officer, Teresa Wheelis(?), is very effective and if it is an urgent situation, the Agency will take the equivalent of a "Dear Doctor" letter, thank you for sending us this interesting patient, you know, the kind of thing that you do all the time, will take that thing, take the forms by fax, provide an IND number on the telephone. That physician calls us back and we can have the medication there by the following morning.

That is how -- now, for others, the medication is stored, you know. Supplies are sent to the Mayo Clinic in Rochester and to Connie, but for others, who have these isolated ones, it happens very quickly. Actually, that is one of the nice things that is nice here to say. The physicians who call are good physicians. They truly are interested in getting something for their patient that won't happen otherwise, but the Agency, whoever understood publicly that the

Agency routinely supplies an IND number on an emergency basis like that. That is not the public perception. It is very nice.

Now, the next slide demonstrates the chemical structure -- and you would expect since we make it we would show it -- 4-aminopyridine is right -- 4 because it is right opposite here, 3,4-diaminopyridine is here. It is unstable. We do ship it cold. The patient doesn't have to carry a refrigerator around with him. The tablets will last a month or so at normal temperature, but not in distribution conditions. That was a good question.

Now, I would like to show the next slide. We have proposed and we proposed kind of before -- we had this system going for another drug in which we gave -- we give away another drug that was not available and now we had -- after having supplied Dr. Sanders and the Mayo Clinic, we thought that we needed to make a commitment to bring the drug to market so that it would be available so that we could put labeling in the PDR, so people would know how to handle it. Therefore, to handle these, we also thought perhaps with all of these isolated INDs roaring in, that it might be helpful to the Agency -- it would certainly be helpful to us to be able to collect all the information and to assemble the safety records,

such as it is.

So, we have proposed to the Agency, and the Agency has not had time to respond, a compassionate Phase 3 distribution program, which I am going to outline to you. We do have an IND and we are suggesting this be extended under our existing IND and there is amongst other things, the patients would be covered if -- more easily, perhaps, than a physician filing their own IND.

Then there is an informed consent, which everybody agrees to and we presented it to the Duke IRB. We wished to present it to the Duke IRB because Duke has Don Sanders on their staff and, therefore, they will have a faculty member, who will really be knowledgeable about the risks and benefits.

Then we have a desire to really collect and be sure. It is a convulsant. We think you need to know an EEG. You need to know a basic electrocardiogram. We have developed suggestions of the reasons why an IND is going to help the progress of the drug come forward.

But to make it easy, we thought that we could do most of the initial stuff on the phone. We need the physician. We need all of the information on the patient because when we distribute the drug, the patient's name is on the bottle, as well as the physician's full name and address. We register the patient and we expect to

receive that same "Dear Doctor" letter that the Agency receives, along with the latest laboratory information or an agreement to collect this information when the patient first comes back to the office.

On the next slide, we have written the entry criteria and I have sent the slides to Don and I have hopes that it is reasonably right, but we do expect -- the big thing in a compassionate distribution program, I think, is to make sure -- it is true in any study -- make sure that the patient who gets into the study has the disease you are wanting to study. We do really insist on that here and in the next slide you will see the pediatric.

We think it is appropriate. The management of the drug is perhaps different in the pediatric patients, but there are patients in Connie Bowe's place who if there is an hour delay in not taking the drug, then the symptoms will again appear. These, she believes, are the entry criteria that she should have for pediatric patients, but we believe that in standard practice these days, pediatric patients should be included.

Now, this is really -- these inclusion and exclusion slides are standard parts of the protocol. They are parts for our existing protocol, which was primarily dovetailed into Duke. This is what we are

expecting to apply broadly and we are planning, however, to put the drug always on top of pyridostigmine.

The next slide shows this exclusion criteria and the next slide. We have rules for this compassionate thing, based on our existing things. We ask that the physician -- if we have to do this fast emergency distribution, there won't be time to get an informed consent because you will shift the medicine and the patient may not be in the office then and so on. So, we ask that the physician start the product only after having had the informed consent signed and in this case obtained the basic entry data.

The tablets are designated only for that patient in a system analogous to the named patient system in the United Kingdom. If that physician has another patient, then that new patient requires another registration. We do receive requests to send sometimes tablets to the patients, but the tablets are sent to the physician's office. There are an occasional -- there are enormous distances in the Midwest sometimes. North Dakota, you can be a thousand miles away from the patient under your care. But we then act as the physician's -- we do that only with established physicians and we act with their -- as their shipping agent.

After one month in this study if the informed

consent has not been received back from us and if the patient has not been benefited or the laboratory data is not up to speed, that patient is out. We have one difference here, which was shown in Dr. Sanders' slide. The proof of continuing benefit, 3,4-diaminopyridine is unusual, very unusual amongst medications. There is no fundamental benefit to it. Maybe helping breathe is an important thing. Improved muscle power is important. There is nothing on the underlying effect of the disease progress.

One can stop the medication and all of the symptoms will immediately return. Start it again and they will immediately go back to where you were before. And this forever and forever, for years and years.

We have proposed -- we had said in our first IND and we have said in our compassionate application, that we think that the proof of continuing benefit is something that actually should flow through to the labeling. That is to say, periodically the patient should be retitrated or perhaps one should take advantage of accidental compliance problems. Went to visit his son at graduation and forgot to take something or missed out on a dose and -- or if there has been no evidence of an accidental non-compliance, then our protocol will require a dose delay, a dose reduction or a dose vacation.

We think by that there will not be a tendency amongst patients to -- that will teach the patient, yes, the medicine is good. That will teach the physician it is good. It will also teach them the opposite. If they don't need it, they don't need to take it.

We have made a very simple scale, a global response. We have pediatric endpoints, which are equally easy to obtain.

Lastly, we think it appropriate because there is a rumor, you know, how can you get 3,4-DAP sometimes. We think it appropriate and we have done it before in the past in other programs, that we let the attending physicians who are liable to receive these patients know of the availability of the compassionate IND. So, when that is approved and when we are set to go, we will do it.

Thank you.

DR. JUHL: Questions. Elizabeth.

DR. MC BURNEY: Actually, I have a comment to make and I want to on behalf of patients that have another disease, called dermatitis herpetiformis. Dr. Jacobus's company has made available at no charge another drug called sulfapyridine and this program has been in effect for a number of years. I have had some patients participate in it now that I know for at least six or

seven years. So that there is a track record here of this type of program working and working very successfully.

I think that should be taken into consideration and I wish to thank you for that.

DR. JACOBUS: Thank you.

DR. JUHL: Questions of the committee? Sir?

DR. SANDERS: I would just like to make a comment about a question that was addressed to me and perhaps I didn't answer it entirely. It had to do with any problems that arose during compounding of the drug before Jacobus began making it as a pill.

It was packaged in capsules by our research pharmacy and during the seven or eight years we used that, we would quite frequently get calls from patients after they had received a supply of the medication asking if we had changed it because they thought it wasn't working as well as it did before or they would tell us, well, you know, you get a super capsule every now and then and some of them are just duds.

We had no way of knowing whether that was true or not. We would have them bring their capsules in. We would analyze it to see if there was any variability. We never convinced ourselves that there was. Whether that is a problem in the compounding or whether that is

placebo effect, I have no way of knowing, but I can tell you that if it is put up in a pill, that is not a question.

DR. GILMAN: I would just like to know whether the company will continue to make this drug available if it is put on the list of drugs that can be compounded?

DR. JACOBUS: We have made it available for nine years or I think nine -- we were trying to discuss, eight or nine years and as far as I know, compounding is possible now and I see no reason -- I think I am neutral on this issue. I think that pharmacy is a very important branch of us and we have pharmacists in our employment. We all depend on pharmacists for dispensing. They are part of the system. I think it is a more difficult thing to do and I think that there is a lot of things pharmacies can do.

I am not sure whether pharmacies want to handle things like this but I think that the advantage of making a systematic way of handling it -- I am neutral on it. I am not an expert in that. I hear the thing -- we will continue to answer your question. We think that we have to collect the data. We think we have an obligation to make it available. We have had our troubles with supplies and manufacturing and all the rest of it.

There is a lot more commitment of the Agency

than when you market it, you know. They will need tons of extra data and the district office visits and -- it is a true commitment. We will bring it forward.

DR. JUHL: I would like to echo Dr. McBurney's comment. It is a pleasure to see a good patient oriented system that has been under operation for a long time. It gives us reassurance.

Help me understand the entrance criteria that you have outlined. Amongst neurologists in the area, are these criteria sufficient to distinguish between patients who have the syndrome and those that don't? Or are you looking for a more severe group of patients with which to collect data?

What I am wondering, are there people who wouldn't make it in to your protocol because of the level of the entry criteria?

DR. JACOBUS: I personally think the answer is "no," but Dr. Sanders is here and his answer ought to prevail.

DR. SANDERS: There might be rare patients who don't meet those entry criteria, but these criteria were actually based on our experience in analyzing these factors amongst the patients that we have diagnosed with Lambert-Eaton Syndrome. But since it is such a rare condition, there may well be patients who have an unusual

form or a very mild form of it. One could then ask whether they would really need this therapy at that point.

I don't know whether those criteria are open to discussion on an individual basis or not. I would think perhaps so. A lot depends upon the experience of the physician in dealing with this disease. There are not many people who see lots of these patients because there are not many of them out there.

DR. JUHL: Few have your level of experience. I am just wondering how many arguments you get into over the criteria at meetings when --

DR. SANDERS: I can certainly envisage a scenario where someone would call me up and say, listen, I have got a patient. I know he has got LEMS because he has got lung cancer and this, that and the other, but he just doesn't happen to make 50 percent facilitation. I would say he has got LEMS. But I don't know whether Jacobus will be able to make that --

DR. JUHL: Thank you.

Any other questions -- oh, I am sorry. Go ahead, Dr. Jacobus.

DR. JACOBUS: Let me add to that that there is built into the trial the patient itself having -- patient having an opportunity to stop and start. It is built

into the informed consent. It is designed -- we originally had a double blind, but not in the compassionate one, so that I think if you have that in as a safety device, then you can allow patients in and see what happens.

So, I think that if a -- I think in our other trial, we have with sulfapyridine, we had originally limited it just to dermatitis herpetiformis, but then there are other conditions that dermatologists use the medication for and we referred those to the Agency and then the Agency said please broaden those things so that we don't have to get all these calls.

I think, actually, with a built-in device, one would tend to allow a trial to see if there was a benefit or not because that is part also of determining the limits of where it works or it doesn't work in writing effective labeling.

MR. TRISSEL: I was glad to hear that it doesn't sound like the cost of the drug would be an issue for patients. It does sound like the cost of transportation to a site might be an issue for patients, who don't have the personal resources to afford that. Am I correct in that?

DR. JACOBUS: It has been more of a problem for Dr. Sanders than it probably would be under the

compassionate IND because we send stuff in a little cooler, like you kind of see at a baseball game. Then we send a call tag the next day to pick the cooler up. So, both of those transports are borne by us. What we say in the informed consent, this draft informed consent, that the Agency has yet to see, is that the patient or the physician or the service or whatever has to bear the cost of the laboratory. We will not cover that in any way.

MR. TRISSEL: So, for patients who have Medicaid or something like that, they are not really eligible for this? There is no funding for somebody in Nebraska to come to Duke to be put on this program and then --

DR. JACOBUS: That is true, but on the other hand, there is no funding from a compounding situation either.

MR. TRISSEL: Well, there are charity hospitals that do provide indigent care.

DR. JACOBUS: Then fine with us. Let them provide it.

MS. JACOBUS: We provide the drug free of charge and the hospital in which the neurologist is affiliated foots the bill. So, it is an indigent program because we don't have a -- we don't charge anything for our compound or the shipping on that.

MR. TRISSEL: Right. And that is different than the previous compound, which the patients have to pay for presumably out of their own pocket.

MS. JACOBUS: I don't know about that.

DR. JUHL: So we don't get confused now, the expanded access that you are proposing would have expanded numbers of investigators so they wouldn't need to come to Duke or to Mayo or they would need to come to Duke or to Mayo?

DR. JACOBUS: They would not come to the main centers to date. The main centers to date have been after us to get the program forward and I have told Dr. Sanders that I think he is actually been instrumental in bringing the drug to a point where we know enough about it that, in fact, it can be considered for development.

DR. JUHL: Good.

DR. SANDERS: Could I just make one point? I want to pick up on the comment made about the hospitals bearing the cost of this. My hospital doesn't bear the cost of this and I don't know that there should be any official expectation that any hospital should take up these costs. These are societal costs.

DR. JUHL: Other questions?

[There was no response.]

Let me first of all apologize for getting us

behind. We are. We should have had the open public hearing at 3:15 and we are almost an hour behind and I apologize both to the committee and especially to our participants in the open public hearing for making you wait.

Let us go to that portion of the program now.

Agenda Item: Open Public Hearing

We have four guests, who will address us on various topics related to the use of compounds. I would ask that each of our guests identify themselves, who they are representing and whether or not they have ties with any of the commercial ventures with whom we have had discussions this afternoon.

First off is Thomas Mick Countee(?), Jr., executive director of the National Spinal Cord Injury Association.

Mick.

MR. COUNTEE: Good afternoon, Dr. Juhl and other members of the committee.

My name is Thomas H. Countee, Jr. I am the executive director and CEO of the National Spinal Cord Injury Association, which is based on Silver Spring.

The National Spinal Cord Injury Association is a 51 year old organization, non-profit organization, with 45 local chapters and support groups from Maine to

California. It is the nation's oldest and largest civilian organization dedicated to helping people with spinal cord injury and disease.

On a personal note, let me tell you that in 1958, as a result of a dive in the Chesapeake Bay, following my sophomore year at Harvard, I suffered a compression fracture at C-5,6 and that rendered me a quadraplegic. At that time, of course, there was no talk about a cure or a therapy for a chronic or traumatic spinal core injury.

You asked me to state whether the organization has any ties to the pharmaceutical companies. Among our corporate sponsors is Elan Corporation. Our corporate sponsors also include Medtronics, Neural Control, State Farm, AS(?) Mutual, a number of other corporate organizations.

Let me go on to say that the main reason I am here today is because the National Spinal Cord Injury Association is, among other things, interested in the health, safety and welfare of our 5,000 members and the more than 250,000 persons with spinal cord injury and disease in the United States. That is our primary interest, not the economic or profit-making interests of any company that is making 4-AP or other therapies associated with spinal cord injury.

The primary mission of the National Spinal Cord Injury Association is to work to empower individuals with spinal cord injury and disease, their families, their caregivers, to make informed choices and to take actions to achieve their highest level of independence and personal fulfillment.

The association accomplishes our mission by three main strategies. The first is to promote, encourage and, where appropriate, fund basic research in central nervous system tissue regeneration. We do that out of three modest restricted research funds and have done so for a number of years.

The second objective is to collect and disseminate information and research relevant to the health, safety and well-being of our members. In that regard, we maintain a Web site, spinalcord.org, that provides comprehensive coverage of news affecting people with spinal cord injury and disease.

News coverage is broadly-based and addresses a variety of vital issues ranging from political events, the legal/bioethical issues, the medical breakthroughs. In addition, our Web site provides up-to-date information on spinal cord injury and disease, national and local events and services.

Finally, the association provides its members

with a quarterly publication, SCI Life, that serves as a repository of information and a forum for the concerns of people with spinal cord injury and disease.

Thirdly, we have, as I said before, about 45 chapters across the country. These chapters provide peer counseling, hospital visitation, spinal cord injury prevention programs in the national population through direct contact with persons who have spinal cord injury or disease, their families and caregivers.

We support the local chapters and we are available to advise them on various political, financial and medically oriented issues. Based on the National Spinal Cord Injury Association commitment to our mission, I would now like to address the issue of the compounded formulation of fampridine or 4-AP.

I would encourage FDA to restrict the availability of this formulation because of the potential negative side effect profile that has been discussed at great length. It is understandable that people with spinal cord injury has been experimenting with and actively obtaining this compound as fampridine has properties that appear to enhance local function, positively affect spasticity, increase sensory function, improve bowel, bladder and sexual function.

These are reasons that such a large number of

patients are seeking the drug. Given this drug's potential to enhance quality of life for persons with spinal cord injury, the joint efforts of Acorda and Elan to successfully market a stable, sustained release compound in compliance with FDA regulations with indications for treating SCI and multiple sclerosis should be fully supported.

Finally, the National Spinal Cord Injury Association believes that the Acorda plan for expanded access should be encouraged by the association and we do so here.

Before I close, let me give you another personal note. In my former life, I was an attorney with Securities and Exchange Commission, Division of Trading and Markets and also the Controller of the Currency. So, I am very well aware of the competing interests of a regulatory agency, industry, consumer advocacy groups, et cetera. I am very sensitive, as I have sat in the place of FDA a number of times in my role at the Controller of the Currency at the Securities and Exchange Commission.

I was also at one time legislative counsel in the White House and as fate would have it, FDA was one of the agencies under my responsibility from the Executive Branch side of the government. I am also the parent of a daughter with bipolar disorder with schizoid aspects.

She takes a drug that many of you are probably familiar with, viprexa(?).

As a parent of a child with a psychiatric disorder, I follow everything that I can on the development of various medications and therapies to deal with the disorder that my daughter has. So, if I sound somewhat passionate about this issue, perhaps you will understand, based on my personal and professional background.

I would request respectfully that you allow Acorda Therapeutics to grandfather in the individuals, who are receiving the compounded drug, to participate in the ongoing clinical trials that Acorda is conducting. Coincidentally, last night in New York in a totally different setting, I had the opportunity to discuss this issue and this upcoming hearing with Donald Ganey(?), the chairman and CEO of Elan and Thomas Mensch(?), the chief financial officer of Elan.

I put the question to them whether or not they were willing to commit resources behind an expanded access study if the compounding -- if the fampridine was not put on the compounding list. They assured me that Elan was prepared to commit such resources. Now, you might say they said that. What do we know about their actual commitment? I don't know. I just say this

because I heard much talk and discussion and questioning earlier about the economics of this proposal and the financial capability of Elan and Acorda Therapeutics to bring this off.

I can only tell what the head of the company said last night.

Finally, should this be approved by FDA, I firmly believe, as does the association, that this would be a major step in the journey towards discovering therapies, which will ameliorate and perhaps one day cure the effects of chronic spinal cord injury and multiple sclerosis.

Thank you for your time. I have brought along the person who runs our resource center, who answers most of the queries that come into the National Spinal Cord Injury Association, Bernadette Morrow, because she is the person who handles the inquiries, some not only membership, but others across the United States, Canada, Europe, even India, who call in asking about 4-AP.

Our last issue of Spinal Cord Injury Life, our quarterly magazine, the title of it was "The Status of Research, A Reason to Hope." There was mention in there about fampridine, 4-AP, and since then we have had a flurry of calls, certainly much more than we normally would have had prior to that issue about the availability

of 4-AP.

I believe, just in the last week, the last three days, Ms. Morrow has had 26 calls about 4-AP. If you have any questions about how patients get answers, to what lengths they will go to get this drug, you can ask Ms. Morrow.

Again, thank you very much for your time.

DR. JUHL: Thank you, Mr. Countee and Ms. Morrow, for being here. Appreciate both your willingness to come before the committee and your patients and even with our lack of an agenda, being on time.

Our next speaker is Gina Ford, who is the executive director of the International Academy of Compounding Pharmacists.

MS. FORD: Good afternoon. It is a pleasure to see you all again. I am Gina Ford, compounding pharmacist, executive director of the International Academy of Compounding Pharmacists.

We are a 1,300 member, not-for-profit association that represents compounding pharmacists in this country. We are solely supported by the membership dues of those members.

Just to touch on something briefly that we talked about last time and that the academy has taken on as a result of requests from this committee is an adverse

drug event program to be able to establish a reporting system of adverse events that might come about through compounded medications and, hopefully, we will have that process in order by the end of this year.

Five years ago, we began a fight for legislation in this country to be able to protect our rights as pharmacists, to meet individual patient needs and to do that in a manner in which we have always talked about, which is called the triad relationship. That is now spelled out in federal law, that we must practice compounding pharmacy within that relationship, patient, pharmacist, physician.

It is very regrettable to me and I feel almost responsible for Dr. Bever's patient, who was left without that relationship of a pharmacist and a physician and that patient to be able to work together to meet the needs of that patient because that is what our goals and our missions are.

That is why I publish that 1-800 number anywhere I can so if a patient has an individual need, they can find a compounding pharmacist in their local area to work with their physicians so that we can solve those problems that they might come across.

Just briefly, I want to touch on the substances. I know that we are running late and I will

be quick.

Some of the statements that were made in regards to the efficacy of 4-aminopyridine were clinically meaningful, modest efficacy or intimation of efficacy. Well, tell that to a patient that it is working for or who can now walk ten steps, who can now dial a phone and ask them if that is a modest, effective dosage that they are on or medication that they are on.

I am concerned a little bit about us looking at the economics of this and not at the patients of this. We are pharmacists and we want to treat our patients. I can think of three products right now that were previously only available from compounding pharmacies, that were then taken through the loop and applied to the FDA and became FDA approved products. We are innovators. We started that.

There is an FDA approved product on the market now and that company is still making money. If a superior product is on the market, we as pharmacists are going to treat our patients with a superior product. So, I just want to make that very, very clear to you. We estimate that in this country there are 11,000 patients on 4-aminopyridine at this time.

I just want to make it very clear that these patients cannot go without this medication. There is no

reason why this medication cannot be included on this list to be continued to have access to this medication and then when a product is brought to the market, if it is approved by the FDA, have access to that as well. I just don't want these patients to suffer in the meantime.

I just don't want these patients to suffer in the meantime. Let's put this drug on the bulk drug substance list and then work with USP to develop standards in which this drug must be compounded. That is certainly an unavailable thing to us right now.

As far as 3,4-diaminopyridine, I appreciate the numbers that were presented to you but there are approximately a thousand more patients in this country that are receiving that drug currently. Dr. Jacobus, thank you very much. That is a wonderful program that you have, but, once again, what if there is a patient in a community and that physician and that pharmacist want to work within that community to meet that patient's need, is there any reason that that patient should have to call across the country to get that medication?

We as a community compounding pharmacist should be able to address that need locally for that particular patient.

I am afraid of some of the issues that the manufacturers are concerned about as far as stability

issues and shelf life issues. That is an area where a compounding pharmacy can fill in. We don't make more medication than what it is going to be stable for.

Can they bring a product to the market that will have the shelf life to make it to the distribution center, to make it to the pharmacy, to sit on the shelf to be then dispensed to the patient? Compounding pharmacies can make products, can store products, can counsel patients with a limited supply so that we are not concerned about the stability issues at that particular time.

We are not afraid of the competition. We welcome a superior product if that is the eventual way that we are going. A manufacturer shouldn't be afraid of our competition. We are here to meet individual patient needs and those patients whose needs cannot be met by those of the manufacturer. That is our purpose and that is what we want to be able to do.

DR. JUHL: Thank you, Gina.

PARTICIPANT: Can I make a comment or raise a question?

DR. JUHL: I would just as soon we proceed with our guest speakers of the open public portion of the hearing.

Our next speaker is Dr. Craig Basch from the

Office of Paralyzed Veterans of America. Dr. Basch.

DR. BASCH: I am Craig Basch. I am with the Paralyzed Veterans of America. I am a neuroradiologist by training. We represent about 70,000 paralyzed veterans that have spinal cord or multiple sclerosis. My role is to be their medical advocate and kind of their advisor.

As far as fiscal relationships, I know that our spinal cord research foundation gave some seed money to Acorda several years ago to start that up. Other than that, I am not aware of other fiscal relationships.

As a physician, I am concerned about the data that was presented here, particularly in light of the variability and the dosages. Those numbers of 50 percent swings in uniformity worried me, particularly the 56 percent increase in dose as it may relate to seizures.

Now, as an imager, I have dealt with seizures in my training in patients who were first treated with the anti-seizure drugs when they came out in a genetic form and seizures are bad news. People fall. They get intracranial hemorrhages. They crash cars. They hurt themselves with heavy equipment and our members are very active and that is a big concern of mine.

Having said that, I also realize that we have a lot of our patients who take this drug, want this drug

and realize benefit from it. When I had my own spinal cord injury, I realized that very subtle changes in neurologic function make a big difference in the patient's lifestyle, which are not measurable on the clinical level. So, that is important.

Weighing those risks and benefits, the official PVA position is that we support the open label method of distribution for our patients as a way that would be reasonably safe and increase your access to the pharmaceutical.

DR. JUHL: Thank you.

Our last speaker in the open session is Jackie Havner.

MS. HAVNER: My name is Jackie Havner and I am 58 years old and I have had MS for 34 years. I have to say that I have been on -- lucky, I was put on a study five years ago of fampridine and I own three wheelchairs and I own multi canes. I still could walk, but I couldn't walk very well and I couldn't walk very far and I couldn't walk without assistance and there were a lot of things I couldn't do.

Now I can lean down and get things off the floor. I can even dance. So, it is really fabulous. While I think everybody should be able to get the medication, I happen to be fortunate I am on the

compassionate use -- in fact, I was really sort of squirming almost, but I just feel that it really needs to be controlled. I was very nervous that I wasn't going to be able to get it and I thought I would definitely go on the pharmacy compounded stuff, but I was terrified. I was really terrified.

I think I would make the analogy of saying I had a husband with cancer and, you know, the difference between MS-IR, which is immediate release and MS-Current, which is continuous release, you know, I could have killed him with the immediate release. On the other hand, he had to have the immediate release to begin with. So, I would say the same thing, kind of -- at least that is how I feel about the pharmacy compounded 4-AP because seizures are pretty horrible things and some of the side effects that I know about that friends of mine have had friends who have experience in this kind of thing, who have been on this because, of course, if you couldn't get it on the study, you wanted to go get it at the pharmacy.

But I really feel that this does not belong on the compounded list, for whatever it is worth, but I really want to see it available because I don't want to get off of it.

Thanks.

If you have any questions I will be glad to

answer them.

DR. JUHL: Thank you very much.

Okay. Are there any other members of the public, who would like to address us, who didn't register with us in the beginning?

I think we will wait until the discussion period. I want to reserve this period of time for the general public.

Seeing none, let me ask the pleasure of the committee. I think our discussion would go probably more rapidly if I didn't ask if you needed a bathroom break, but I will do that anyway. Do you want to take two minutes or are you ready to proceed with the discussion?

MR. BASCH: Just one last comment.

My comments about the open label, which is to support the Acorda-Elan expanded process. That was clear, I think, wasn't it? Yes, I thought so.

DR. JUHL: Break or no break? Help me out here.

Okay. We have two people that want a break and more that don't. So, we won't.

Let's go to the discussion portion.

**Agenda Item: Discussion and Vote on
Neuropharmacological Drug Products**

Shall we do last in, first out? In my mind,

the 3,4-diaminopyridine is more recent in my mind. Let's do that one first and then move to the aminopyridine. Okay?

Let me try and summarize and, again, start leading us as far as we can go and see what I think you think.

One, we have a serious illness. Secondly we have a drug that shows some promise and certainly has some effect for some patients. We have a need for more information. We have in all likelihood some questions of drug stability and so on. This is a difficult to compound product and it requires refrigeration. We have a company who has an in-place distribution program that they are volunteering to make a wider access program from.

Are all those parts of the things that we understand we understand? Then it would seem we are at the question that is similar to what we had this morning is to recommend that the drug be listed on the bulks list available for pharmacy compounding or that the drug not be listed on the bulks list with the recommendation that the FDA pursue the expanded access program with the manufacturer and doing as they would normally do, make sure that those patients who are on the drug now are not disadvantaged.

DR. LIEBMAN: Question, please.

DR. JUHL: This, too, we would like to hear back on how the progress is in the development of a program by our fall meeting.

Yes, David.

DR. LIEBMAN: Did I understand that there are another thousand patients out there?

DR. JUHL: Yes.

DR. LIEBMAN: Can the manufacturer, can Jacobus pick up a thousand patients, a thousand additional patients. If we make it unavailable through compounding, will Jacobus have the ability to pick up a thousand extra patients?

DR. JACOBUS: We probably have two-thirds of that population now of sulfapyridine that Dr. McBurney spoke about. It is easier to ship.

I would like to ask Dr. Sanders whether there really are that many out there. We have no indication of that. We certainly technically could do it. Right now, we are paying the full cost on it and probably -- I don't contemplate that expense with any degree with pleasure.

DR. LIEBMAN: I guess my thought is there were a thousand patients --

DR. JACOBUS: Technically, the answer is easy. Yes. Money-wise, it is always hard because we survive

only on what we sell.

DR. LIEBMAN: How do we move those thousand patients who are currently getting medications through compounding and their physicians into your system with a fair amount of smoothness.

DR. JACOBUS: The patient would have to see the physician. Presumably, the compounding doesn't take place absent a physician's script.

DR. LIEBMAN: Correct. I would imagine -- of course not. You can't compound without a physician's prescription.

DR. JACOBUS: I hope so.

DR. LIEBMAN: Yes.

DR. JACOBUS: I don't know whether those -- we don't have any intimation that there is that kind of a requirement out there.

The physician then has to call and say I have this patient. Here are the data. The patient should be registered and we will register the patient and ship the medication the next day.

The physician will not be allowed a refill unless we receive the data that everything is squared away. That is our proposal. If there is a great backlog of patients that we wonder about, whether the diagnosis is true, then I think we might require all the

information in first, but we do expect to receive from the physician a letter comparable to what a physician will write a family practitioner on returning a patient or the physician will write to the Agency transmitting the information we expect to receive before we will ship clearcut report that the patient has the diagnosis.

If the patient is already on it, we would expect to receive evidence that the patient needs to stay on it. In other words, there might be patients that got on it just because of awareness and desperateness and no follow-up. 3,4-diaminopyridine can be stopped and very few patients will be -- I mean, they will be weaker, but very few patients are dependent on breathing machines and they will be -- I don't think there are that many patients. If there are, we will do it.

DR. JUHL: Does that answer your question?

DR. LIEBMAN: My only thought is that a reasonable expectation. Are you going to have 500 doctors or 700 doctors across the country now writing letters requesting that the patient --

DR. JACOBUS: Well, we had that in sulfapyridine. We had 10 percent of the American Academy of Dermatologists participating in that program. And the answer was it was a real squeeze at the start.

DR. LIEBMAN: I only raise the issue. It is

not a question of you can or you can't. I just raise the question. That is all.

DR. JUHL: Sarah.

DR. SELLERS: I just wanted to clarify that we are still under the assumption that another IND could be obtained from a physician for this use or for another use or another indication or are we saying that the only way to obtain this drug now would be through --

DR. JUHL: No. Another IND is always possible.

DR. SELLERS: Okay.

DR. JUHL: Loyd.

DR. ALLEN: Just for clarification, as we look at this then, we have a system which has been in operation for x number of years, where the material is available through Jacobus, number one. Secondly, it is available through compounding pharmacies. This is all ongoing until the point in time that we will have a commercially available product on the market.

I guess my concern would be changing what has been reasonably effective for these patients that are out there, possibly putting them and their physicians into an area requiring extra effort when with the 3,4-DAP, we have not seen any significant safety or efficacy concerns from the patient's standpoint. I am not sure that it would be necessary to change what is ongoing until the

point in time that the product is commercially available.

DR. JUHL: I think the argument is and it is a valid argument that by moving many more patients onto the protocol, your safety data would be collected more rapidly and it would speed the product's approval rather than delay it.

If you look five years out and, say, okay, the drug is approved today, we will know more about it. I think there is that advantage that counterbalances that.

I think your point, though, too, is good. Is there enough time between now and then to -- the bureaucracy changeover will cause some struggle for a period of time. My suspicion is it will take long enough for this drug to get approved that there will be a real advantage to having a greater number of people in the safety database because right now, unfortunately, the compounded products, there is no data collected on those patients and I was impressed with the requirement and your stick-to-itiveness on getting the data back in order to provide drug.

Dr. Gilman.

DR. GILMAN: We have heard from good authority that the drug is effective. We have also heard a good deal about its safety with respect to at least those patients who have been treated with doses lower than 80

milligrams per day. So, I think the real question is whether additional data are needed with respect to safety.

Would it be better to have an IND and not allow the drug to be compounded, so that there would be a central distribution site, central provider for the drug and an enforced requirement essentially that all concerns with the drug, all seizures be reported? I think that is really what it amounts to because it certainly sounds safe.

MR. TRISSEL: It sounded to me like the burden, whatever there is, is going to fall largely on Dr. Jacobus and his group because they will be all coming in. It doesn't sound like the burden on a physician with one or two patients is particularly severe to get on the program.

DR. JUHL: Dr. Katz and then Dr. Rodriguez.

DR. KATZ: Again, with regard to safety, I guess we heard that where -- that the patients who were receiving it through compounding, we haven't heard any problems about them, but that is part of the problem. We haven't heard. There is no obligation on anybody's part who would be treating those patients with compounding, that they report any problems.

They are not in the system. So, again, just to

reiterate, one of the great advantages of having this all subsumed under an IND is that there are reporting requirements and we will -- and physicians will be required to follow the patients closely and report bad things that happen.

So, right now I would say of the patients who were under the INDs, we know there really aren't any problems below 80 milligrams or whatever dose. But in patients outside the IND, however many there are, we really have no idea what the experience has been.

DR. RODRIGUEZ: First, let me say up front I like the idea of the data collection in an organized fashion. This is going to make a 7 1/2 fold increase in the shipment of this drug compared to what you have got at this moment, but you possibly have proven that already in another system. This drug is going to be prescribed only by neurologists, I would assume, because the one concern that I have is those -- maybe it is small, 5 percent, 10 percent, who are now receiving their medication, whose forms are not being filled up and, therefore, no form, no drug.

Now they are getting the drug and the question is what recourse do those patients have then? Storm the neurologist's office?

DR. ALLEN: Just one real quick question I had

when Dr. Jacobus was doing his presentation on dosage modification or dosing adjustment, how many strengths is the DAP available in?

DR. JACOBUS: Right now it is in 10 milligram strength with a -- it is a scored tablet. So, that gives you options.

DR. ALLEN: Okay. Thank you.

DR. JUHL: I wasn't sure that I understood Dr. Rodriguez's comment or if I was expected to respond to it, but I must confess that I didn't quite -- if he wants to ask it again, I am totally interested.

DR. RODRIGUEZ: No. I just had a question, first of all, about the increase, which was 7 1/2 fold, but I figured that -- Ray has shown that you could do it at least with the previous study. My study was what percentage of patients might be put at risk.

DR. JUHL: I remember.

Remember one other thing, too, I think --

DR. RODRIGUEZ: In your past experience with the previous drug, what was the percentage of people that were not turning in or you had to call and say if you don't send me the medication, you don't get the drug? In other words, what were the outliers that did not send the information?

DR. SANDERS: It occurs.

DR. JACOBUS: There was an element of your question, though, that was relevant. There are, for example, doctors of osteopathy, who may not be members of the American Academy of Neurology, who have a strong interest in the subject and are totally competent. There are some -- there is an analogous groups to the American Academy of Dermatology and we allow those -- and there are some general practitioners, who we think are absolutely clear on, at least in dermatitis herpetiformis it is a relatively rare disease, but they are skilled that way.

So, we make it -- we have in the past -- perhaps I shouldn't say that in the presence of all these Agency people, but we have said and we have written it into the other protocol that the invitation is to the members of the professional academy, but if there is somebody who has produced the data and is managing the patient, we think that is fair enough.

We accept the patient. We often -- they will send us a C.V. and a license and we will send them the mint.

DR. JUHL: Other questions or comments or opinions?

If it is absolutely necessary -- I would like to limit discussion to the committee.

DR. SANDERS: It is not absolutely necessary, but I would just like to comment on the referral patterns that I would predict would happen with DAP if it were made available under this program. And I think I have some expertise in that.

This is a rare disease. Not many physicians ever see it and very few are very comfortable dealing with it. I would predict that most neurologists in practice would prefer to refer a patient with this condition to someone who has seen a few patients with it. So, I think probably what would happen, if it were not available to any physician who could write a script is that they would find who in their local community or nearby had dealt with these patients, refer them to them and let them deal with the issue of getting the drug.

DR. JUHL: Are we ready for the question? Are we clear on the options? Option 1 is to recommend the drug be listed. Option 2 is we recommend the drug not be listed. All those favoring Option 1, please raise your hand. I see four hands raised.

Those preferring Option 2, please raise your hand. Seven for Option 2. So our recommendation with a split vote is that the drug not be listed and the FDA pursue the opportunity to have an expanded access program that would serve at least as many patients that are on

the drug now.

Shall we move to 4-aminopyridine. We have the same kinds of issues with this drug. We have, I think, with this drug more evidence of difficulty in the compounding of the product, but we have less information on the company's ability to put the program into operation and it would be from my guess a bigger program to put in operation because of the numbers of patients.

We had some discussion about whether or not there is a thousand patients to be dealt with Lambert-Eaton. Are there, indeed, 10,000 patients that would need to be dealt with for 4-aminopyridine?

Do you have an estimate of --

DR. COHEN: None of the figures are definite now, just because of the nature of the fact that people are getting at the compounding. So, there aren't really records, but from a number of different sources, Elan actually commissioned a market analysis group to look at this a few years ago. I think there are other -- we have had input from various physicians who have in turn worked with some of the compounding pharmacies. Our best guess now, just based on all of these different inputs, which seem to agree with one another, is that that there probably are 10,000 or so and perhaps more than 10,000 people, who are using compounded formulations now. Those

numbers are in all likelihood increasing now as the publicity surrounding the work, the clinical development and so on and some of the spinal cord injury and multiple sclerosis advocacy groups are getting word out, just tracking what is going on.

So, our sense is that it is likely to be around 10,000. It is possibly more than 10,000 and the numbers are probably growing. I should also tell you that we have -- in response to some earlier questions, we have looked at the logistics for supplying this for up to 20,000 so far, based on our sense of where things are. We are quite comfortable that together with Elan we can supply that in an expanded access study. Again, that doesn't mean that that is what the number would be and I will also reiterate that we need to work closely with the FDA to discuss with them what the regulatory parameters are around such a study.

But in terms of our capability and our desire to supply this, we have already done the math, as it were, on up to 20,000.

DR. JUHL: Could you contrast and compare how you envision your distribution program with that of Dr. Jacobus?

DR. COHEN: My sense is that we are talking about two very different animals. Again, I am by no

means an expert on Lambert-Eaton Syndrome or the demographics of that syndrome, but based on that data that have been discussed here today, in the case of Lambert-Eaton, we are talking about a population that numbers apparently in the hundreds. It is a truly very rare condition.

The issues in distribution, therefore, may or may not be comparable because in the case we are discussing with multiple sclerosis and spinal cord injury, clearly, we are talking about, as I said, 10,000 or on that order of magnitude and, again, from our perspective, we certainly are not equipped as a company nor is Elan and nor would I say are many, even major pharmaceutical companies equipped on their own to run these kinds of studies. These are special circumstances and even in the cases of some of the major pharmaceutical companies who ran studies for HIV drugs, expanded access studies for HIV drugs and so on, they worked with some of the contract research organizations that we are also talking with now.

So, from our perspective, this is very much manageable, using an expert group that is outfitted to do this and has experience in doing it and really our obligation in that case is to work closely with them to exchange the appropriate information, to supply the drug

in the appropriate form, which we can do with Elan as our partner and then to collect the data from them and assimilate it and pass it on to the agency under our IND.

MR. CATIZONE: I would speak in favor of not listing this product on the list of substances approved based solely on the safety data presented by the FDA prior to this meeting. I am uncomfortable accepting the data that was presented at this meeting regarding the compounded products by pharmacists because I feel that that data may be biased and unfair.

I am also disturbed by entities, which hold patients hostage and this committee hostage in situations where patients can be at risk and would commit that NADP would urge its members and work with its members to take whatever legal actions it could to ensure that patients' medications and therapies would not be interrupted in situations like this.

DR. GILMAN: I think there is a big contrast between 3,4-DAP and 4-AP, with respect to both efficacy and safety. The studies with respect to efficacy are highly questionable with respect to how good this medication really is, how much function do patients, most patients, really get. They may show some improvement on a scale. That doesn't mean that any but the unusual patient is really that much better with the medication.

And we are hearing about very variable levels of blood levels and dosage levels that provoke seizures. Here, I think, we really need systematic, carefully collected data with good reporting with respect to adverse events, as well as efficacy.

So, this one is much more clearcut from my perspective than DAP. I think this certainly ought not to be on the list.

DR. JUHL: Other comments?

Are we ready for the question?

DR. COHEN: Could I make one more comment in response to something that was said?

You know, the term "holding patients hostage" was used earlier and I certainly don't want to get into an escalation of that particular debate. I do want on the record to say that at the end of the day, we at Acorda and Elan are interested in the welfare of our patients. We have very strong relationships with the community patient groups, who work in this area. You have heard from some of them today. There are others out there. We try to be as responsible and good citizens in this regard as we possibly can in terms of supplying them with information about what we are doing and doing the right thing.

I just wanted to illustrate for the committee

or for the panel one illustration of why this is for us not so clearcut in terms of how and when, under what circumstances one supplies patients with an experimental compound. I will tell you and I will go out somewhat on a limb because we have not yet submitted this to the FDA, but I do want to try and share this with the panel, that in our studies, even in chronic spinal cord injury, we were very surprised to find -- these were placebo controlled, double blind study -- we were very surprised to find the extent to which patients apparently experienced remarkable benefits under placebo, never having had the drug at all.

I am talking about people who were injured for five years, who suddenly one week opened their hand for the first time and grabbed a glass of water. I am sure that all of you have the same response to this that we did, which is as soon as we saw it before we broke the blind, we said my goodness, that is fabulous. We have just a remarkable drug effect here.

There was no question that it was placebo. There was no mistake. The blood levels, the plasma levels showed it. It was the same sequence. So, I think when we are talking about how we address our patient population here and taking into account their welfare, I just want to put a plea out that we all remember that

these things in clinical medicine are hardly ever cut and dried and one sees remarkable things that one would never imagine you would see under other than the influence of the drug itself, but you do see it.

So, we want to be as careful as possible. Frankly, the idea of investing tens of millions of dollars to try and get a drug approved that we may or may not be able to get approved is not -- it is not the most appealing occupation in the world, but we are doing it because we do believe in the drug. We believe we will be able to show these things, but we also believe we need time. We need to do the right studies. We need to cooperate with the Agency and we need to do it in the right way and that putting this drug out ad lib for anybody in an uncontrolled fashion is not going to be doing anyone any favors and least of all our patients.

So, I just wanted to put that on the record. Thanks.

DR. ALLEN: 4-AP is similar to the 3,4-DAP. It is not the anybody is putting something out there. It has been out there for years, in fact, 10 or 11,000 patients are on it right now. Again, what this does is it alters their method of obtaining the drug, whether or not they can obtain it. That would be one of the things, you know, that I would be concerned about.

DR. JUHL: Seeing no more questions, let's call the question with the same two options. Option No. 1, recommendation to list the drug on the bulk compounding list. Option No. 2, recommend the drug not be listed and ask that the FDA would pursue an expanded access program for the drug that would not inconvenience patients who are already receiving it.

MR. TRISSEL: Dr. Juhl, just one point for clarification.

If we vote for the latter option and the program does not materialize, what recourse do we have at that point because now we voted to put it on this list and the program that we were banking on didn't happen. Is there an alternative to that?

DR. JUHL: I believe that the FDA would pursue something and not just let the patients all go wanting.

DR. BEHRMAN: Again, as I tried to say before, we believe there are two questions here. One, is it appropriate for the list and that question has to be answered. Then if the answer is "no," you have our assurance that we will make every effort that patients who need access -- that doesn't necessarily mean everyone who wants it, but depending on the appropriateness, the safety of the drug, et cetera, we will make every effort to make sure that such a program is in place. Again, the

Agency cannot require programs.

I can think of very few companies that have initiated large programs this early in development, but it has been done and has been done successfully.

DR. JUHL: Ready? Okay. Those who favor Option No. 1, please raise your hands. We see two votes. Those favoring Option No. 2, raise your hands. Nine favoring Option No. 2. Okay.

We are six minutes over budget. Again, for those members of the staff who weren't here earlier, I want to thank you for the efforts that you put in preparing us for today's meeting and certainly my thanks to the committee for bearing with us, as well as those guests who made presentations to us.

The committee will adjourn and meet again tomorrow morning at 8:30.

[Whereupon at 5:06 p.m., the meeting was recessed, to reconvene at 8:30 a.m., the following morning, Friday, May 7, 1999.]

ABOUT	I'D	RIGHT
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ALL	I'VE	S S S
ALREADY	IF	
ALSO	IN	SAID
A	IS	SAY
AND	ISN'T	SHE
ANOTHER	IT	SHOULD
ANSWER	IT'LL	SO
ANY	IT'S	SOME
ANYTHING	ITS	SOMEPLACE
ARE		SOMETHING
AS	J J J	
AT		T T T
	JUST	
B B B		THAT
	K K K	THAT'S
BE		THATS
BECAUSE	KNOW	THE
BEEN		THEIR
BEFORE	L L L	THEM
BUT		THEN
BY	LET	THERE
	LIKE	THEREFORE
C C C	LOT	THESE
		THEY
CAN	M M M	THINK
CAN'T		THIS
CORRECT	MADE	THOSE
COULD	MAKE	TO
	MANY	TOO
D D D	MAY	
	MAYBE	U U U
DEPOSITION	ME	
DID	MEAN	US
DIDN'T	MISS	
DO	MR	V V V
DOES	MRS	
DC	MS	VERY
DC	MUCH	
	MUST	W W W
E E E	MY	
		WANT
ELSE	N N N	WANTS
		WAS
F F F	NEED	WE
	NO	WE'VE
FAR	NOPE	WELL
FOR	NOT	WERE
FROM	NOW	WHAT
		WHAT'S
G G G	O O O	WHEN
		WHERE
GET	OF	WHICH
SO	OFF	WHO
GOING	OK	WITH
HOT	OKAY	WITHIN
	ON	WITNESS
H H H	OR	WOULD
	OTHER	
AD	OUR	Y Y Y
ADN'T	OUT	
AS	OVER	YEAH
AVE		YES
AVEN'T	P P P	YOU
E		YOU'D
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ERE	PUT	YOU'VE
ERS		YOUR
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'HEART(1)[89,3]	1999(10)[9,20][11,15][15,7][15,15][15,19][15,25][84,20][88,2][97,11][97,13]	4-AP(29)[9,25][10,2][10,4][141,20][143,21][143,24][145,5][149,3][149,4][149,22][153,20][172,21][176,17][207,23][208,5][208,9][208,10][208,15][219,11][224,21][241,13][243,4][246,5][246,9][246,11][246,13][253,19][269,14][272,12]	ABANDON(1)[39,10]
'WAKES(1)[90,10]	1ST(1)[15,25]	40(3)[60,13][88,23][133,16]	ABBY(1)[6,16]
-----	-----	409(1)[131,5]	ABDOMINAL(3)[130,23][134,1][139,7]
-EATON(5)[128,9][132,3][132,17][132,8][133,5]	2	42(1)[141,5]	ABILITY(10)[67,10][79,2][119,5][119,10][177,19][179,6][191,16][191,22][256,14][266,3]
-----	2	44(2)[59,11][148,4]	ABLE(48)[33,10][33,16][65,3][71,23][81,20][96,18][111,12][111,13][115,2][122,8][124,20][133,11][144,8][144,8][144,18][145,2][145,3][145,5][145,7][152,5][152,20][166,11][168,22][178,12][183,5][184,23][184,24][192,19][192,21][192,21][192,25][193,1][199,10][199,20][206,10][218,20][220,19][227,24][236,11][247,11][247,16][248,1][250,5][250,25][253,5][253,9][272,1][272,3]
.001(1)[28,13]	2,4-(1)[20,15]	45(5)[30,4][83,17][130,4][240,14][242,18]	ABNORMALITIES(1)[137,18]
-----	2-DICHLORO(1)[21,14]	47(2)[40,3][142,12]	ABOVE(7)[53,18][85,10][85,20][85,24][89,10][146,2][175,8]
0	2.5(1)[197,5]	475(1)[141,23]	ABSENCE(2)[52,11][52,11]
-----	20(12)[9,6][49,3][59,12][74,8][83,8][85,10][130,3][155,7][208,5][211,3][212,3][218,19]	5	ABSENT(1)[257,10]
0.5(1)[129,19]	20,000(2)[267,7][267,17]	5,000(3)[197,25][199,11][241,9]	ABSOLUTELY(9)[72,5][112,16][112,16][122,24][170,23][199,20][264,6][264,21][264,23]
00(2)[126,11][126,13]	200(1)[106,15]	50(16)[28,3][33,13][47,11][47,12][49,6][59,3][74,6][106,15][122,1][151,19][155,2][205,11][205,17][205,22][236,10][251,20]	ABSORBED(4)[23,10][39,15][43,17][129,1]
02(1)[127,1]	204(1)[139,2]	500(2)[106,16][258,20]	ABSORPTION(2)[25,24][43,11]
06(1)[274,10]	208(1)[4,8]	503(12)[8,17][9,2][11,5][11,11][12,16][12,25][14,8][15,22][16,12][16,16][16,18][16,21]	ABUSE(3)[86,7][86,8][86,11]
-----	21ST(9)[14,17][15,6][15,7][15,15][15,19][97,11][97,13][122,4][123,9]	51(1)[240,14]	ACADEMY(23)[17,20][35,2][61,25][62,4][62,7][69,25][71,5][71,5][79,14][83,3][87,7][91,4][116,16][116,20][117,1][117,12][246,23][247,2][247,9][258,24][264,2][264,5][264,13]
1	22(2)[141,1][141,4]	52(1)[141,5]	ACAM(4)[87,10][87,16][87,20][87,20]
-----	23(2)[139,10][178,14]	53(6)[23,11][39,15][39,22][40,1209,14][209,20]	ACCEPT(4)[72,7][72,20][93,18][264,16]
1,300(1)[247,4]	23RD(1)[9,20]	55(1)[126,12]	ACCEPTABILITY(1)[21,25]
1,500(1)[204,4]	24(5)[39,24][39,25][141,10][212,1][221,14]	56(1)[251,21]	ACCEPTABLE(10)[29,21][37,2][47,7][58,25][63,4][80,22][104,14][124,21][125,6][162,25]
1-800(1)[248,4]	24(5)[39,24][39,25][141,10][212,1][221,14]	58(2)[47,9][252,20]	ACCEPTED(3)[18,14][96,2][195,13]
1-CHLORO-2,4-DINITROBENZENE(1)[20,15]	25(7)[64,3][66,9][67,1][150,19][154,24][197,4][212,12]	59(3)[12,14][59,1][138,18]	ACCEPTING(1)[269,2]
1-CHLORO-2-NITROBENZENE(1)[22,3]	250(2)[122,1][136,18]	5FU(1)[36,15]	ACCESS(46)[93,2][93,4][96,25][119,23][120,6][122,17][122,17][123,3][167,21][168,4][168,24][170,2][170,25][172,23][173,10][173,13][173,17][176,25][177,11][177,11][177,18][178,2][179,12][179,12][181,14][184,3][191,14][192,22][198,14][198,17][198,22][199,18][221,16][238,21][243,24][245,8][249,10][249,12][252,15][255,17][255,24][265,21][267,10][268,13][272,23][273,15]
1-CHLORO-4-(1)[22,2]	250,000(1)[241,10]	6	ACCESSED(1)[93,6]
1-MONOCHLORO(1)[21,13]	26(3)[130,9][210,19][246,13]	60(5)[10,24][122,1][130,16][163,17][212,16]	ACCESSING(1)[202,17]
1/2(3)[154,25][262,12][263,12]	29(2)[58,25][178,14]	65(1)[59,2]	ACCIDENTAL(4)[137,17][142,13][231,18][231,21]
10(22)[63,19][83,17][97,22][129,13][129,14][144,17][154,24][156,23][194,14][195,6][195,13][200,3][200,22][212,21][212,22][214,25][218,2][221,14][258,24][262,17][263,3][272,14]	2CDA(2)[104,18][110,16]	68(2)[131,14][138,25]	ACCOMPLISHES(1)[241,21]
10,000(6)[266,8][266,21][266,21][267,4][267,4][268,6]	3	7	ACCORDANCE(1)[4,8]
100(2)[197,4][197,6]	3,4-(4)[203,19][203,22][207,5][225,8]	70(4)[30,5][59,3][129,7][155,7]	ACCORDING(3)[108,13][110,20][194,21]
104(3)[140,3][142,5][148,3]	3,4-DAP(7)[203,25][207,23][208,11][232,8][259,24][269,14][272,12]	700(1)[258,21]	ACCOUNT(2)[12,19][271,17]
11 6,12][142,22][152,10][20,10]	3,4-DIAMINOPYRIDINE(12)[127,16][150,24][151,15][203,13][203,14][206,21][207,15][227,8][231,3][249,19][255,5][258,13]	7TH(2)[8,24][84,20]	ACCOUNTABILITY(2)[167,13][167,15]
12(4)[129,8][133,4][133,10][163,22]	3.3(2)[157,9][193,18]	8	ACCREDITED(1)[29,16]
120(2)[41,12][218,3]	30(20)[1,1][64,5][66,9][95,14][95,19][95,25][96,1][96,3][96,7][98,13][133,22][133,23][139,11][145,23][212,3][212,16][219,15][224,15][274,9][274,11]	8.8(1)[156,24]	ACCUE(1)[68,12]
127(2)[8,18][174,16]	300(2)[132,23][134,6]	80(5)[212,5][215,4][219,20][261,2][262,7]	ACCUMULATE(1)[210,20]
12A30(1)[4,13]	34(1)[252,21]	85(2)[47,8][214,2]	ACCUMULATION(1)[134,18]
13(1)[47,1]	35(4)[49,4][129,20][130,14][141,22]	86(1)[9,22]	
130,000(1)[85,9]	35,000(1)[198,24]	87(1)[58,25]	
134(1)[46,24]	350(1)[136,18]	8TH(2)[11,14][11,15]	
135(1)[25,7]	36(4)[29,22][133,21][139,22][151,3]	9	
136(1)[142,2]	37(2)[46,25][46,25]	9.2(2)[157,9][193,19]	
14(1)[58,16]	38(1)[29,6]	90(2)[141,22][183,1]	
140(4)[141,23][142,12][142,12][145,23]	39(2)[217,9][218,9]	94(1)[29,6]	
15(7)[75,5][131,8][155,2][200,3][210,12][212,22][239,17]	3TC(1)[198,25]	98(3)[21,12][21,17][197,2]	
15.6(1)[156,24]	-----	99(1)[197,2]	
16(3)[19,7][141,7][141,7]	4	A	
161(1)[129,25]	4-(11)[128,6][129,8][131,3][136,6][138,9][141,11][142,18][142,23][149,7][153,19][249,5]	A	
18(4)[4,8][22,23][29,24][46,10]	4-AMINOPYRIDINE(25)[127,16][128,1][128,12][128,16][128,16][128,22][129,4][129,14][130,8][130,21][131,19][131,23][133,1][133,20][134,4][138,4][139,18][142,15][146,11][149,16][153,10][227,7][248,12][265,24][266,9]	A	
1875(1)[20,18]	-----	A.M.(2)[126,12][274,11]	
190(1)[9,20]	-----	A.M.(1)[1,1]	
.958(1)[240,19]	-----	AA(2)[109,12][109,18]	
.980(1)[58,14]	-----		
.983(1)[46,10]	-----		
.984(3)[18,14][207,17][224,14]	-----		
.986(1)[60,10]	-----		
.988(1)[209,13]	-----		
.989(3)[133,3][150,16][219,14]	-----		
992(2)[129,7][218,18]	-----		
996(1)[162,3]	-----		
997(1)[194,22]	-----		
99 1,14][15,6][18,17][88,9]	-----		

5][43,12][57,11][67,20][115,11][130,22][144,21][146,16][154,9][156,1][156,22][157,8][157,16][165,6][171,25][209,17]

ALTOGETHER(1)[179,18]

ALWAYS(18)[63,11][65,17][65,20][110,12][123,6][126,5][182,6][182,21][188,24][198,20][198,20][216,15][229,25][247,18][257,2][259,11]

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AMELIORATE(2)[104,3][245,22]

AMENDMENT(2)[16,19][120,18]

AMERICA(4)[87,9][88,8][251,8][251,10]

AMERICAN(15)[18,16][35,2][61,25][62,4][62,7][87,9][91,4][91,13][116,15][116,20][117,1][117,12][258,24][264,2][264,4]

AMES(8)[22,16][27,19][43,6][43,9][56,17][66,5][81,1][105,12]

AMID(1)[180,20]

AMINO(2)[200,13][200,14]

AMINOPYRIDINE(12)[128,7][129,9][131,4][136,7][138,10][141,12][141,13][142,24][149,8][153,20][249,6][255,6]

AMINOPYRIDINES(3)[128,4][128,6][134,14]

AMONG(3)[212,7][241,1][241,8]

AMONGST(9)[70,9][71,6][72,3][21,6][228,5][231,4][231,25][235,3][235,17]

AMOUNT(9)[8,2][80,14][100,14][124,4][126,3][174,20][174,25][221,19][257,7]

AMOUNTING(1)[19,7]

AMOUNTS(4)[42,3][55,6][194,16][261,10]

AMPTITUDE(3)[208,17][208,18][21,1]

AMUS(1)[138,5]

AMST. AM(1)[138,24]

ANALGESIC(1)[6,25]

ANALOGOUS(6)[24,18][44,13][58,20][130,8][230,12][264,4]

ANALOGY(1)[253,12]

ANALYSIS(13)[42,12][42,25][55,23][56,12][103,20][103,23][125,10][156,15][157,11][195,20][197,1][197,15][266,15]

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ANALYZED(3)[101,23][186,3][187,10]

ANALYZING(3)[16,2][192,20][235,16]

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AND/OR(1)[212,18]

ANDERSON(6)[2,10][94,25][104,19][106,14][108,1][110,14]

ANDREW(4)[127,13][144,15][161,4][161,6]

ANECDOTAL(9)[30,20][72,16][74,14][76,7][142,14][144,5][146,10][149,10][170,8]

ANECDOTALLY(1)[74,9]

ANECNOTE(1)[142,20]

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ANIMALS(4)[17,18][141,18][215,15][267,22]

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ANNOUNCEMENT(2)[3,19][88,9]

ANNOUNCING(1)[89,9]

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ANTI-INFLAMMATORY(1)[6,25]

ANTI-RETROVIRAL(1)[31,16]

ANTI-SEIZURE(1)[251,25]

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ANTICIPATED(1)[162,13]

ANTICONVULSANT(1)[17,19]

ANTICONVULSANTS(3)[149,10][149,12][149,24]

ANTIGEN(1)[66,17]

ANTISEPTIC(1)[18,7]

ANTIVIRALS(1)[31,5]

ANTONELLI(1)[60,10]

ANXIETY(1)[139,8]

ANYBODY(8)[75,19][111,4][113,4][118,24][200,11][200,18][272,7][272,13]

ANYBODY'S(2)[69,8][261,21]

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ANYONE(8)[19,19][37,6][64,1][109,4][172,19][219,22][220,4][272,8]

ANYWAY(3)[110,3][151,5][254,17]

ANYWHERE(4)[40,3][49,6][212,12][248,4]

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APART(2)[184,3][197,18]

APOLOGIZE(6)[136,13][181,23][193,2][200,4][239,15][239,18]

APPARENT(4)[28,5][46,13][58,19][163,18]

APPARENTLY(10)[17,17][35,15][45,7][67,19][68,9][89,24][142,13][145,22][268,1][271,4]

APPEALING(1)[272,1]

APPEAR(13)[9,16][11,6][14,3][15,12][34,16][55,5][64,25][90,22][92,2][143,12][155,4][229,16][243,11]

APPEARANCE(2)[3,22][4,3]

APPEARED(3)[32,22][86,4][140,6]

APPEARING(1)[84,19]

APPEARS(11)[13,19][18,20][22,17][41,15][41,21][88,9][90,4][95,5][123,2][143,13][147,22]

APPLICABILITY(1)[63,21]

APPLICATION(13)[13,15][24,20][24,21][25,19][28,19][30,18][54,9][58,4][95,24][121,1][168,14][175,5][231,14]

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APPRECIATE(10)[5,21][28,20][62,7][82,19][126,8][173,15][176,18][193,5][246,19][249,19]

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APPROACHED(1)[139,16]

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APPROPRIATE(27)[26,2][38,7][38,7][84,22][110,23][122,7][168,5][169,6][172,20][178,2][191,2][196,7][196,14][198,19][198,20][199,1][199,7][199,13][199,25][225,6][229,12][232,7][232,9][241,23][268,20][268,21][273,12]

APPROPRIATELY(3)[108,15][143,17][170,16]

APPROPRIATENESS(1)[273,16]

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APPROVED(30)[13,15][27,3][27,4][31,16][45,19][51,12][51,13][51,21][52,1][52,5][58,10][85,23][87,18][90,11][98,10][100,1][143,20][169,9][174,7][175,5][232,13][245,19][248,24][248,25][249,11][260,10][260,16][268,25][271,25][272,1]

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APPROVING(2)[95,9][95,9]

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AQUEOUS(1)[56,7]

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AREA(21)[3,8][10,15][37,22][38,21][63,4][63,20][63,21][72,23][78,25][105,15][124,11][139,24][185,17][194,24][195,12][202,11][235,3][248,6][250,9][259,24][270,14]

AREAS(9)[36,21][44,16][49,5][60,18][60,19][60,19][63,22][68,5][141,15]

AREATA(51)[26,14][26,22][27,2][27,6][27,12][28,2][28,8][28,24][29,5][29,20][31,22][33,12][40,10][45,14][45,25][46,9][46,11][47,5][47,23][47,24][48,24][50,16][50,20][58,14][58,16][58,24][59,16][60,13][60,17][60,19][61,1][62,9][62,21][63,5][63,21][63,24][64,6][64,20][65,13][69,16][70,11][71,20][72,17][73,18][76,9][81,21][99,25][102,12][117,13][117,15][117,20]

AREN'T(12)[12,19][52,5][52,17][53,12][78,1][78,7][79,25][173,18][176,23][177,21][262,6][266,13]

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ARMS(4)[65,8][130,4][204,10][210,12]

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AROUND(18)[1,10][6,1][33,21][41,12][53,7][63,19][64,4][64,25][102,17][106,16][106,24][145,5][185,15][193,5][224,12][227,10][267,3][267,13]

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 COMPARED(9)[59,10][60,10][75,2][75,4][114,17][150,5][213,24][216,9][262,13]
 COMPARES(1)[49,3]
 COMPARING(1)[211,7]
 COMPARISON(3)[41,7][55,1][190,10]
 COMPASS(1)[170,17]
 COMPASSIONATE(10)[182,3][214,7][228,2][229,7][230,2][231,14][232,12][236,20][237,17][253,6]
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 COMPLEMENTED(1)[214,5]
 COMPLETE(5)[30,4][54,5][223,17][223,17][223,19]
 COMPLETED(4)[14,20][163,7][209,16][210,18]
 COMPLETELY(2)[122,10][129,6]
 COMPLETENESS(1)[25,10]
 COMPLETION(1)[91,18]
 COMPLEX(1)[98,23]
 COMPLEXITY(1)[5,9]
 COMPLIANCE(11)[3,4][3,5][6,23][7,4][7,8][7,10][161,23][168,19][196,3][231,18][243,19]
 COMPLICATED(4)[68,11][111,10][180,13][221,1]
 COMPLICATION(1)[217,24]
 COMPLICATIONS(1)[170,3]
 COMPLY(2)[201,2][201,8]
 COMPONENT(1)[9,4]
 COMPONENTS(1)[11,9]
 COMPOSITE(1)[130,11]
 COMPOSITION(1)[188,25]
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 COMPOUNDED(69)[11,10][12,1][13,22][15,23][81,5][91,25][92,18][94,2][103,6][104,9][104,22][135,18][142,23][143,9][145,10][145,10][152,10][156,13][157,17][158,21][159,20][160,9][160,14][161,13][163,23][164,8][164,17][166,20][167,7][168,10][168,21][170,14][170,22][172,21][174,14][176,8][176,9][176,19][176,20][177,25][179,23][184,15][184,21][184,23][185,11][186,4][187,17][188,23][189,3][192,24][1

95,1][197,10][200,9][201,7][201,10][201,12][222,10][234,1][243,3][244,25][247,12][249,17][253,10][253,19][254,1][260,19][261,6][266,22][269,3]	2,14][167,10][178,7][182,12][197,3][248,18][250,8][250,17][251,18][272,18]	21][239,5]	CONVULSANT(1)[228,15]
COMPOUNDS(2)[15,4][188,3]	CONCERNING(7)[11,18][12,11][14,7][32,20][32,25][69,24][164,2]	CONSIDERING(7)[28,23][51,22][82,17][86,18][191,3][202,8][222,3]	CONVULSION(4)[133,10][134,2][134,7][134,8]
CONCERNING(153)[1,5][1,19][2,25][7,3][7,21][9,2][10,20][11,5][12,24][13,13][13,16][13,18][14,19][15,16][15,17][16,8][16,10][16,16][16,22][16,24][17,1][17,21][18,10][19,17][19,22][20,19][22,1][22,5][32,3][38,7][42,21][67,9][70,6][74,19][77,14][79,6][79,7][84,17][84,21][84,24][85,14][86,7][86,8][86,11][86,15][86,19][86,22][86,24][87,1][87,3][87,8][87,8][88,3][88,8][88,12][89,3][89,5][89,13][89,15][90,6][91,1][91,2][91,3][91,5][91,19][91,22][94,15][97,15][104,15][105,1][106,6][106,25][107,17][110,7][112,11][124,8][125,5][125,6][125,8][127,21][134,16][135,14][135,15][142,16][145,12][148,15][153,17][153,21][153,23][154,15][156,15][157,15][158,3][158,18][168,3][168,15][169,20][170,4][174,9][174,14][175,1][175,4][176,17][177,15][177,24][179,17][180,17][183,5][186,23][187,6][190,5][190,18][190,19][193,18][194,1][194,15][194,22][196,4][196,9][196,21][200,19][201,3][201,6][220,14][220,19][233,7][233,21][234,4][238,5][245,9][245,10][246,24][247,1][247,3][247,5][247,21][248,6][248,22][250,4][250,10][250,15][255,22][257,6][257,9][259,18][261,22][266,2][266,13][266,19][272,21]	CONCLUDE(1)[72,18]	CONSULT(2)[8,11][196,5]	CONVULSIONS(8)[129,22][131,15][132,8][134,4][134,9][134,11][134,12][135,20]
COMPOUNDS(34)[4,15][4,23][5,13][8,1][14,6][14,22][19,21][25,14][36,17][37,11][42,1][51,19][53,23][54,1][55,15][62,1][67,14][81,4][81,6][81,7][91,17][92,10][105,4][106,5][110,10][113,1][113,19][115,9][178,4][201,25][201,25][203,15][203,17][239,24]	CONCLUDE(5)[13,7][30,16][31,11][162,21][173,19]	CONSULTANT(1)[88,7]	COOLER(2)[237,17][237,19]
COMPREHENSIVE(1)[242,6]	CONCLUDES(1)[19,25]	CONSULTATION(1)[16,5]	COOLING(2)[137,24][138,1]
COMPRESSION(1)[240,21]	CONCLUDING(1)[181,13]	CONSULTATIVE(2)[30,13][31,4]	COOPERATE(1)[272,5]
CONCENTRATED(2)[28,10][46,19]	CONCLUSION(9)[36,7][47,6][60,17][143,10][145,20][145,24][210,5][214,1][216,14]	CONSUMER(5)[2,4][85,8][193,21][226,10][244,6]	COOPERATION(1)[115,1]
CONCENTRATING(1)[11,3]	CONCLUSIONS(7)[31,6][32,1][36,3][36,23][37,3][48,2][59,20]	CONSUMERS(1)[88,1]	COPIES(6)[4,10][11,15][11,17][14,9][174,17][174,23]
CONCENTRATION(12)[28,15][90,16][139,20][142,3][143,12][145,21][147,15][147,21][155,1][160,2][208,9][225,11]	CONCLUSIVE(1)[171,24]	CONTACT(5)[24,19][74,17][91,3][224,11][242,22]	COPY(2)[88,2][89,2]
CONCENTRATION(12)[28,15][90,16][139,20][142,3][143,12][145,21][147,15][147,21][155,1][160,2][208,9][225,11]	CONCOMITANT(1)[149,9]	CONTACTED(1)[91,5]	CORD(44)[128,21][130,7][130,9][130,17][131,6][150,8][150,10][151,11][154,5][161,18][161,22][163,3][163,8][163,9][163,18][164,7][181,6][240,5][240,11][240,13][240,17][241,7][241,10][241,14][241,15][241,17][242,7][242,12][242,17][242,20][242,22][243,2][243,9][243,16][243,22][245,23][246,1][246,6][251,12][251,15][252,7][266,25][268,5][271,1]
CONCENTRATIONS(5)[22,7][28,12][145,23][220,15][220,20]	CONCUR(1)[60,23]	CONTAINED(1)[157,9]	CORE(2)[138,1][240,24]
CONCEPT(2)[79,13][88,17]	CONDITION(10)[112,15][167,23][204,2][204,8][204,19][211,14][212,7][235,18][265,6][268,2]	CONTAINER(3)[155,16][156,10][158,7]	CORPORATE(3)[241,2][241,2][241,4]
ONCERN(40)[31,18][33,18][35,14][37,2][37,23][40,14][43,1][49,10][51,5][53,23][56,12][82,20][94,11][110,13][111,11][112,21][114,15][119,18][122,6][131,3][132,1][134,13][150,2][167,14][170,11][170,11][170,22][170,22][176,2][176,3][176,6][176,6][180,7][191,16][213,18][215,13][215,14][252,4][259,21][262,16]	CONDYLOX(1)[26,9]	CONTAINERS(1)[214,19]	CORPORATION(3)[153,14][162,1][241,2]
ONCERNED(21)[31,15][42,7][49,2][62,10][69,10][74,7][101,21][119,7][119,7][16	CONFESS(1)[263,9]	CONTAINING(3)[11,12][11,14][12,9]	CORRECTED(3)[215,19][215,20][215,23]
	CONFETTI(1)[44,15]	CONTAINS(3)[12,14][21,13][21,18]	CORRECTLY(4)[95,20][135,7][201,12][222,8]
	CONFIDENCE(2)[159,12][178,11]	CONTAMINANT(1)[43,8]	CORRELATION(2)[133,7][140,7]
	CONFIDENT(3)[61,8][191,22][199,22]	CONTAMINANTS(2)[56,21][57,14]	CORRESPONDS(1)[160,22]
	CONFIDENTIAL(2)[160,10][189,8]	CONTEMPLATE(1)[256,23]	CORTEX(3)[11,20][11,24][146,9]
	CONFIDENTIALITY(2)[189,24][189,25]	CONTENT(6)[156,21][156,23][156,23][156,25][157,6][157,18]	CORTICAL(3)[146,14][146,21][146,24]
	CONFIRM(2)[41,6][54,25]	CONTENTS(2)[198,10][198,11]	CORTICOSTEROID(4)[45,21][63,17][64,6][75,3]
	CONFLICT(4)[3,14][3,18][3,20][4,3]	CONTEST(1)[75,3]	CORTICOSTEROIDS(3)[26,24][40,11][63,11]
	CONFUSED(1)[238,20]	CONTEXT(1)[188,21]	COSMETIC(8)[8,18][12,16][26,5][26,19][31,23][47,25][52,25][59,17]
	CONFUSING(2)[31,11][216,4]	CONTINUATION(2)[59,3][59,19]	COSMETICALLY(3)[29,20][47,7][58,24]
	CONGENITAL(1)[223,10]	CONTINUE(22)[10,22][28,1][50,10][71,23][75,2][96,12][101,5][133,11][148,17][152,5][165,24][166,4][166,13][166,16][168,12][169,1][175,19][180,6][184,22][214,21][233,25][234,15]	COSMOS(2)[6,13][6,13]
	CONGRESS(1)[175,9]	CONTINUED(4)[31,24][142,22][156,8][249,10]	COST(10)[168,7][173,19][187,5][214,12][237,11][237,12][237,23][239,9][239,10][256,22]
	CONNECTION(2)[89,4][89,14]	CONTINUING(4)[168,21][176,5][192,24][214,20]	COSTS(3)[172,20][239,12][239,12]
	CONNECTIONS(1)[204,20]	CONTINUOUS(1)[253,15]	COTTON(1)[76,24]
	CONNIE(2)[226,21][229,14]	CONTRACT(5)[197,15][201,22][202,3][202,12][268,14]	COULD'NT(12)[71,11][109,16][109,17][118,11][145,8][152,13][171,16][252,24][252,25][252,25][253,2][253,23]
	CONSENSUS(1)[34,10]	CONTRACT(4)[21,17][51,21][267,18][269,13]	COUNSEL(2)[244,10][250,16]
	CONSENT(9)[182,8][182,21][228,8][230,6][230,9][230,24][236,19][237,21][237,21]	CONTRIBUTE(2)[81,25][86,25]	COUNSELING(1)[242,20]
	CONSEQUENCES(1)[51,15]	CONTRIBUTING(1)[8,6]	COUNT(2)[31,8][31,12]
	CONSEQUENTLY(1)[181,1]	CONTRIBUTION(1)[104,5]	COUNTER(4)[240,4][240,8][240,10][246,18]
	CONSIDER(17)[5,8][5,13][19,16][19,23][63,16][70,4][84,18][89,8][91,23][99,24][102,14][121,17][158,16][189,11][207,3][216,23][224,10]	CONTROL(11)[29,14][29,15][78,24][111,7][141,25][147,15][147,21][148,25][163,20][204,15][241,3]	COUNTERBALANCES(1)[250,11]
	CONSIDERABLE(3)[124,4][155,1][188,22]	CONTROLLABLE(1)[172,10]	COUNTRIES(1)[90,14]
	CONSIDERATION(6)[10,10][10,12][13,4][15,3][97,14][232,25]	CONTROLLED(24)[29,13][30,7][47,17][47,18][49,23][59,6][72,8][92,22][129,3][138,12][138,25][139,20][139,20][140,19][142,3][163,16][164,4][171,24][172,8][174,1][208,15][209,5][253,8][271,2]	COUNTRY(19)[90,12][106,16][106,25][109,14][112,11][112,13][147,9][178,10][198,17][206,20][207,21][225,15][242,19][247,5][247,16][249,5][249,21][250,2][258,21]
	CONSIDERED(8)[10,20][10,25][14,1][20,23][129,17][153,20][206,	CONTROLLER(2)[244,4][244,8]	COUPLE(17)[1,6][36,16][67,3][69,18][77,13][97,4][141,25][146,10][149,14][152,11][183,20][197,13][200,23][201,22][209,15][217,5][217,6]

