sort of terminal elimination. If you do it with two-compartment modeling with this kind of data you always get a very long half-life, also because of the sensitivity of the radioactivity measurements that you do. So, the actual half-life would be much smaller. The first interval would only be three weeks.

DR. FARRAR: My understanding is that the company either has or is about to submit an indication for pediatrics as well. Is that right?

DR. VAN DEN DOBBELSTEEN: Yes.

DR. FARRAR: So, I think your point is well taken. I think it would be useful to hear what kind of things will be looked at to assure some sort of safety. I mean, part of it is that the drug is sequestered there.

The next question is does it matter and I think there is just a hint of some data from the rat experiments that there is some weakening of the bone, but it is only minor.

DR. BRAY: Dr. Farrar, we have Dr. Genant here but I did want to let you know that we did recently submit our pediatric development plan to the FDA. It was our intent to first establish safety and effectiveness of sugammadex in

the adult patient population before we move forward in conducting pediatric trials. Again, we did recently submit a pediatric development plan to the FDA for their review and comment before we initiated those studies. Dr. Genant, maybe you want to comment on the safety.

DR. GENANT: yes, I think it is important to keep in mind that while this agent does go to the bone, to hydroxyapatite, it does not have an extremely high affinity for bone such as, for example, technetium bisphosphonate. Bisphosphonates go with a very high affinity. In this case only about on the order of 15 percent, 10-15 percent of an administered dose will actually go to the bone. It may even be less than that, 5-15 percent.

So, we don=t have an agent here that predominantly goes to bone. We have just established the fact that the half-life, indeed, is not really the 270 days because it is down to about half that at the end of about three weeks but then there is a tail that is extended.

I think it is also important to kind of look at all of the 15 preclinical trials that have examined the bone effects. I think you would see that with these bone effects, in fact, generally do not demonstrate a significant

difference, and only in a minority of cases was there a significant difference.

In the young adult model bone strength was comparable, and the other bone parameters were comparable. In the juvenile model actually some of the parameters with micro-CT showed an advantage to the drug and some did not. So, it was a bit of a balance.

So, I just want to point out that if one looks at the entire picture with regard to the bone effects that there are things that need to be further clarified, and they will become clarified as the pediatric study goes forward, but I think that we need not be at the level of alarm given the fairly extensive preclinical data that are available.

DR. VAN DEN DOBBELSTEEN: One further comment I would like to make, to sort of put this safety margins into perspective, is that the magnitude of the safety margins that we have shown for effects on bone and teeth are really way out of scale if you compare to what cyclodextrins would be traditional targeting, and even in our clinical data on human safety we don=t see any effects on renal safety which would be a more sensitive organ as compared to bone. So, it would be more appropriate to monitor and that is what we

will do.

DR. FARRAR: Other issues or questions that people would like to discuss? The next step here is to go the questions for the committee and I just want to point out that when we are discussing amongst ourselves these questions we are not actually able to ask for additional clarification. So, if there are points that you want clarified, you should do that now.

DR. BOEN: Would the committee perhaps be interested in the views of our clinical experts with regard to immediate reversal and the capacity of sugammadex in playing a role there?

DR. FARRAR: Dr. Nichols, are you interested in this particular topic? Dr. Pollock? I think we are okay with regards to that.

DR. NICHOLS: I wanted to go back to the nonclinical findings in bone and teeth from Dr. Wasserman, if he is still here. This is your slide number 4, on page number 2. You write that the relationship of femur size to decreased body weight possible through micro-architectural findings does not temporally correlate preceding decreased body weight gain. I just wondered if you could comment on

this decreased body weight gain. Is that in both groups? Why did that occur? Do you know? Or, are we supposed to infer anything important from the body weight gain issue?

DR. WASSERMAN: In a particular study I believe that the explanation for the decreased body weight gain was ascribed to general toxicity of the compound at high doses. In the nonclinical data it was not uncommon to see at higher doses some suppression of body weight gain. Therefore, this is not a terrifically unexpected finding in this study. You know, the reduction of femur sizeB-you know, one could say, well, it is a chicken and egg sort of scenario.

You know, maybe you have decreased growth leading to decreased body weight gain. The microautoradiography data doesn=t appear to show any distribution to the growth plates that would likely affect the growth. So, the sense of this is that this is just an effect of the drug that is not directly related to toxicity here.

Actually, I think to be fair, if memory serves, there may have been some reduction in ulnar length as well earlier in the study that could also have something to do with that as well, but there were clearly some effects on

the trabecular bone. It is unclear. That may represent a decreased growth rate issue or slight immaturity of the skeleton. Does that answer your question?

DR. NICHOLS: Yes, it is helpful. Just to clarify, you are saying that the administration of the drug in these cases was at a high dose so that you would expect some toxicity in terms of growth, development and weight gain and you are not really concerned that it would be an issue at clinical doses or clinical use doses.

DR. WASSERMAN: Well, again, there was a no effect level identified that does provide some safety margin, and there are, as I said, clear indications in other nonclinical studies that the body weight reduction even in adult animals is observed as well. So, it would not necessarily be related, strictly speaking, to a negative effect on growth. The pre- and postnatal studies that were done did not, I believe, pick up reduced growth. So, I think that also sort of plays into that as well. But, again, we are still reviewing the data so our conclusions at this time are still preliminary.

Questions to the Committee and Recommendations

DR. FARRAR: Any additional questions? Just a

point of clarification, I misheard my instruction. You are able to get some clarification during the discussion session but it has to be very limited. It can=t involve presentations, and so on. So, if there is a question that comes up that we need clarification on, we can ask either party. If there aren=t any other points of discussion maybe we will move to consideration of the questions. For those of you who are not paying attention to the agenda, we are zipping right past the break which isn=t supposed to happen for another half an hour. Perhaps trying to deal with some of these issues earlier in the afternoon than we might otherwise I think probably would be a good thing for all of us.

So, questions for the committee, the first question, the applicant has conducted a clinical trial to evaluate the efficacy of sugammadex to effect the immediate reversal of neuromuscular blockade. The primary efficacy endpoint was the time from start of administration of rocuronium bromide or succinylcholine to the recovery of T_1 to 10 percent of its baseline value. Sugammadex was administered to patients 3 minutes following administration of RCB.

Question (a), does the primary endpoint have clinical relevance? If no, what other endpoints might be more useful?

Question (b), based on the data submitted from this study, is there sufficient clinical information to assess whether sugammadex, when used with RCB, provides a clear advantage when confronted with the Acannot ventilate/cannot intubate@ situation in the clinical setting? If not, what additional information would be required to assess a possible role for sugammadex in this scenario?

We will first have discussion on question (a), does the primary endpoint have clinical relevance? If no, what other endpoints might be more useful? I am going to actually ask for specific comments from all of you about this.

DR. EISENACH: Well, the clinically relevant endpoint would be to take a healthy volunteer, give them an induction dose of anesthetic, paralyze them, give them this drug and see when they start to breathe again. That is not something that we would ask anyone to do. It is a very ethically complicated question to ask. Studying this in the

emergency setting is almost impossible. The T_1, you know, is that clinically relevant in the presence of an induction dose of anesthetic which probably potentiates the drug effect? I think it is really hard to say, and the FDA must have had meetings with the applicant trying to decide what kind of endpoints are appropriate.

I think it is really hard for us as a committee to say. My personal opinion is that this is a clinically relevant endpoint. I think providing more information, which the applicant has actually done, which is to say how much time to 0.1, to 0.5, to 0.9 provides us with a better sense of at least the neuromuscular blockade reversal part of this whether it is clinically relevant. That is my two cents on it.

DR. POLLOCK: I would agree that it is as clinically relevant as probably anything we can come up with in an ethical scenario. I mean, you could measure other things but I don=t know that anything else that you could really measure would have anymore clinical relevance.

DR. FARRAR: Dr. Nichols?

DR. NICHOLS: Well, I asked the question whether everybody started breathing after getting this drug and I

was told yes. So, that is really the relevant endpoint for me. It would be great if the applicant could show a slide that provided some data to support that statement but I think if this was a secondary endpoint, spontaneous respiration after receiving the drug occurred promptly, that is where I get reassurance.

DR. DESHPANDE: Just reading the question when these were sent to us, I asked myself if I would extubate somebody if I knew that the patient had reached a ratio of 10 percent. So, that to me, as Jim said or David said, is a clinical outcome. So, specifically to this question, the ratio is really not of clinical relevance. It is relevant to the discussion that we are having today but would you extubate somebodyB-I will ask Dr. Nussmeier, if I told you that this patient had reached this ratio would you extubate?

DR. NUSSMEIER: When I read this question I thought it would be much more clinically relevant to have 0.7, 0.8 or 0.9 but, fortunately, that data has been provided so I was somewhat reassured as I continued to read the background material. It would be interesting to have the data presented regarding the other clinically relevant endpoints that they did collect, such as head lift or five seconds.

We didn=t actually see those slides. It would be nice to see with any of the trials.

DR. SORIANO: To plan the devil=s advocate, we are saying clinical relevance and the question here is whether or not the neuromuscular blockade has been reversed. Obviously, many of us used different cocktails of anesthetic drugs to induce a state of anesthesia in our patients and the duration of that varies with what we use. So, thinking about it scientifically, that is the only thing you can measure if the question is to see if neuromuscular blockade is adequately reversed. In this case adequate would be 0.9. Right?

I mean, those are my two cents and to start throwing in all these confounding variables, just the types of anesthetics we use or the depth of anesthesia we use up to the point of reversal may make the question.

DR. EISENACH: Yes, so if you think of the broader question of what information should be shared with the clinician, I think the time to reaching 0.1 is probably not a very important number to the clinician. I think the time when you would expect reasonably strong efforts to overcome an obstructed airway by the patient is probably more than

0.1. You know, in this case these are parallel numbers that are moving and are very close together, the 0.1, 0.5 and 0.9. But I think you would want to present to the clinician a number very much closer to 0.9 than 0.1.

DR. FARRAR: let me ask those who do anesthesia, it was suggested before that the clinical test of squeezing your hand or lifting your head was actually more relevant to a sort of level of 0.5 or 0.6. Is 0.9B-I mean, obviously, that is the area where people are able to swallow and the airway is better protected but I am wondering in terms of the clinical utility of the drugs that are used in the ER whether, in fact, you use the clinical signs of the patient being able to perform certain activities, and whether some data on when patients achieve that level of arousal would be useful.

DR. SORIANO: Well, you are confusing two things here. You are considering arousal or the state of anesthesia versus the level of neuromuscular blockade. I mean, certainly you can have a patient under 1 MAC of isoflurane anesthesia with a 0.9 reversibility of the Train-of-Four but I wouldn=t extubate his trachea or her trachea. It is not responsive. So, if you are just talking about

head lift, hand grip, it is also indicative of depth of anesthesia that the patient is under.

That is why we have to rephrase this question in saying that we have to really look at the degree of neuromuscular blockade, rather than this whole issue about clinical relevance, because the clinician can rule out the effect of neuromuscular blockade as a cause of the patient=s morbidity at the termination of the anesthetic.

DR. FARRAR: So let me ask the question differently. The specific question here, especially part (b) which I guess we will get to in a minute, is the Acannot intubate/cannot ventilate@ situation.

Clearly these patients are getting other anesthetic agents at the same time as they are getting the neuromuscular blockade and I wonder if it would be useful to think, in terms of the outcomes we are talking about, whether there is additional information that the FDA might want in terms of understanding the relative efficacy of this drug versus other drugs.

It sounds like, from what I can hear, that we are talking about the T_4/T_1 ratios at a level something above 0.5, so 0.6, 0.7, 0.8, 0.9. It is obviously very hard to do

the study. The times when it is actually necessary to do this are very rare and getting patients in studies would be very difficult.

So, I guess in response to your question, it would seem that there are lots of other factors involved here, and is there a guidance that would be really different than the guidance that is given with succinylcholine or other things for this particular drug?

Are you going to address something different?

DR. MILLER: Yes, just very briefly. I just thought I would make two or three comments. First, please recognize what the implications of a very profound block, a non-depolarizing nerve block is. It is virtually impossible now to reverse it. Now we can.

The second point is to get into what you were talking about, the T_1 versus T_9 versus whether you have head lift, and so on and so forth. I think the T_1 is clinically evaluable because when you are in a profound situation the T_1 signals that it is likely we are now on the way of recovery. That is really the first signal that you have that might equate with the beginning of diaphragmatic movement.

Then, when it gets to T_9 it encompasses all of the clinical measures you might use to assess neuromuscular blockade. So, the T_1 really says, okay, I am a little bit reassured, even though that is not enough I am a little bit reassured that reversal is actually going to happen, and then the T_9 of course is the gold standard, as you already recognize. So, that is the way I view th picture and I though I would just make a comment on that.

DR. FARRAR: Dr. Prough?

DR. PROUGH: I think really the answer to the second question seems to me to be implicit in answer to the first question. It is hard to imagine what additional data would be helpful. It is clear that you can give a relatively large dose of a non-depolarizing muscle relaxant and if you decide you need to abruptly reverse it, you can do that with really pretty substantial rapidity. It is hard for me to see what additional information would be necessary to expand on that.

DR. FARRAR: Dr. Simone?

DR. SIMONE: Perhaps I can put this question into a little bit of a different perspective, the way we were looking at it in terms of getting advice from you folks.

The first part of it relates to the primary endpoint, which is this return to T_1 to 10 percent of baseline. What we want to get a feel for is whether you believe that the comparison for sugammadex to succinylcholine based on that would show you whether sugammadex is truly superior in reversing muscle relaxation sufficiently to beat succinylcholine.

The second part relates to the first in that does reversal of neuromuscular blockade alone offer benefit? Is there any evidence to suggest that it offers benefit in terms of rescuing a patient from the Acannot ventilate/cannot intubate@ situation? Or, are there other factors that need to be taken into consideration?

So, what we are trying to understand here is have they adequately demonstrated that sugammadex is superior to succinylcholine in terms of recovery from neuromuscular blockade, and does such recovery really impact on the ability to rescue from Acannot intubate/cannot ventilate?@

DR. EISENACH: How many people around the table have been in that situation, and the reason the patient survived is that the succinylcholine wore off? I know I have been in that situation in obstetrics a few times back

20 years ago.

Anyone else been in that situation? My impression is that it does happen and, despite having given the anesthetic induction drugs, the reason that patients have survivedB-again, this was in an era without the kinds of airway devices that we have currently--was that succinylcholine wore off, and this has the potential of being a minute or two faster than that, which is a minute or two which is a long time. That is an important minute or two I think.

So, I don=t think you can answer the question scientifically but having been in that situation before, that minute or two can be very important. I don=t think 0.1 is adequate for a 450 pounder, who has lost their upper airway and you can=t ventilate, for them to start breathing.

So, I don=t think 0.1 is the number that we would want to give the clinician but I believe the reversal of deep neuromuscular blockade after a rapid sequence induction by itself is intrinsically worthwhile.

DR. PROUGH: Obviously, the comparison study with succinylcholine is a rapid sequence type of induction scenario and I agree with Jim this is faster than the

spontaneous recovery with succinylcholine in that situation. But, in fact, I suspect that most people now, if they get into a Acan=t intubate/can=t ventilate@ situation it actually occurs after neuromuscular blockade with a non-depolarizer.

It is in a situation where they didn=t expect the airway to be difficult and in fact it is. So, there is an even more striking comparison between sugammadex and the current situation, which is in the current situation you can=t do anything if you have given a non-depolarizer and a profound block.

You really are stuck with a Acan=t intubate/can=t ventilate@ situation until you can do something mechanical to try to provide gas exchange. Sugammadex gives you another option.

DR. FARRAR: Dr. Pollock?

DR. POLLOCK: I think one of the things that I am a little bit hung up on here is the complexity of the clinical situation as we have talked about because what happens in my practice is not exactly like the bar graph here where we give sugammadex.

We stick an LMA in before the sucs wears off and

then the patient wakes up. I mean, the complete inability to not intubate and not ventilate is an extremely rare scenario and when that happens we are going to put an LMA in.

I think for me, it is maybe a semantic thing, the use of the term Aclear advantage.@ I think there definitely is an advantage. To me, it seems more like yet another alternative, something you add to your armamentarium that you can use to help take care of these difficult patients. But I think definitely it is something that we have not had previously that we can use. So, does that mean clear advantage? I guess.

DR. FARRAR: Dr. Nussmeier?

DR. NUSSMEIER: Well, again, with respect to the Acannot intubate/cannot ventilate@ scenario, the avoidance of a prolonged period of apnea and/or hypoxemia is also dependent upon so many other factors and I think that is what all of us, as clinicians, are struggling with.

You know, it would also be dependent on the induction agent that was chosen and the dose of the induction agent that was chosen, on whether there were comorbidities like upper airway abnormalities or pulmonary

insufficiency that were present in this patient.

My take away from the materials that were supplied was that this agent does provide some superiority with respect to other neuromuscular blocking agent alternativesB-well, with some caveats because it may not in patients who have renal failure or severe renal insufficiency.

I think we are all a little leery of a cavalier approach that particularly our younger colleagues may be tempted to adopt because the combination of rocuronium and sugammadex may not necessarily be better than other approaches, for instance, awake fiberoptic intubation in all patients considering all other comorbidities.

So, I think it would need careful postmarketing surveillance to see how it all shakes out, and careful education to avoid some sort of cavalier broad acceptance of a technique in patients who may have difficult airway and other comorbidities.

DR. FARRAR: Dr. Nichols?

DR. NICHOLS: I just want to try to restate my opinion in reference to Dr. Simone=s query about Acan=t intubate/can=t ventilate.@ When that scenario-Bwell, let me just backup.

I am persuaded, as I think the rest of the panel is persuaded, that the reversal to T_1 at 10 percent with sugammadex is superior dissipation to succinylcholine=s effects. That said, the Acan=t intubate/can=t ventilate@ scenario, if you use the recovery of T_1 what you are saying is that this is a surrogate marker of being able to ventilate or breathe spontaneously because that is what is going to keep the patient alive. The stronger way to answer this question is to be clear that that is, in fact, going to be the end result after reversal with sugammadex.

DR. FARRAR: Dr. Simone?

DR. SIMONE: Would it be possible to poll the committee for whether or not based on the efficacy information alone that they have been presented with, would they be willing to take succinylcholine off their cart and use rocuronium bromide along with sugammadex if they are confronted with a patient where they are concerned about airway management? If you are not willing to make that trade, what else would you want to know to convince you to do that?

DR. POLLOCK: Well, that is not a fair question because they have already told me that if I have

accidentally reversed my patient and I have to re-intubate him I can=t use rocuronium and I have to have sucs so I can=t take it off my cart. Sorry.

DR. SIMONE: Would you go to the rocuronium before you went to the succinylcholine initially? I think the contention is that this has the potential to actually replace succinylcholine and I am trying to get a feel for whether you folks agree with that, or if you still have some hesitation and, if so, what would it take to convince you.

DR. EISENACH: Well, as an obstetric anesthesiologist, that is why I asked about pregnancy because the situation that we are most interested in is the unanticipated difficult intubation. Sometimes we anticipate it might be difficult but the alternative is bad also, and you might make the decision to do rapid sequence.

But obstetrics is an area where unanticipated difficult or impossible intubation is much more common so, since we have no idea about the dose that might be required in a pregnant woman at an emergency Cesarean section under general anesthesia, I don=t know what to do if this label says it is better than succinylcholine because I don=t know if the dose that they have studied is appropriate to a

pregnant patient.

Her intravascular volume is larger. This is largely restricted to intravascular volume. Succinylcholine doesn=t last longer in a pregnant patient because pseudocholine esterase levels drop. But if they didn=t it would last a shorter time. So, the dose required for sugammadex may be greater. I don=t know.

So, it doesn=t provide me guidance in the exact population that I, as an obstetric anesthesiologist, a very small part of the anesthesia world, am interested in. But I think it is an important one for the scenario of failed intubation.

DR. FARRAR: Dr. Deshpande?

DR. DESHPANDE: I will make two points. One is on the T_1. I think as a clinician if I hear that the drug is better at T_1 it is not really going to help me with knowing, as Dr. Nichols pointed out, whether the patient is breathing or not.

So, I think Dr. Eisenach brought this up in earlier discussion, that it would be more helpful if you said that 95 percent of patients are fully reversed at such-and-such a point, or a more applicable point which we are

more familiar with in the clinical realm, which is the 0.7 or 0.8 or even 0.9. So, I think that is the first question.

The second part of the question, coming back to Dr. Simone=s query, is there aren=t pediatric data so from a pediatric standpoint, similar to the obstetrics, we can=t say we are going to replace succinylcholine. As a matter of fact, for the second or potentially the third go around in a difficult situation we are stuck with having sucs as the only drug available. So, if everything bears out this is a potentially very useful medication as one of the armamentarium but not as the sole part of the armamentarium.

DR. NUSSMEIER: Again, we are also stuck for the moment with alternatives in patients who are on dialysis until further studies are done so it would be premature to forget about the alternatives.

DR. FARRAR: So, if I could just summarize here and make sure that I understand this correctly, with regards to point (a) in terms of the clinical relevance, everybody agrees that it is a point that has validity in terms of demonstrating differences between drugs, but that in thinking about trying to treat patients there are other endpoints that are much more clinically useful in terms of

the point at which the patient begins to breathe, a ratio of 0.7, 0.9, and in many ways the clinically relevant endpoints are different and the T_1 at 10 percent is not by itself clinically important.

In terms of question (b), the second issue thereB- I am sorry, just to finish up with (a), additional data on some of those other endpoints, some of which were presented but some of which were not presented would be useful.

With regards to the Acannot ventilate/cannot intubate,@ I think there were a number of points made. As a non-anesthesiologist, what I heard was that there are lots of factors that go into this decision about how you then treat patients that you have difficulties with.

Dr. Eisenach suggested that years ago, anyway, reversal with succinylcholine going away in a way that reversed the neuroblockade was a key factor in potential for survival in patients. I also heard that there are other much more advanced techniques in terms of how you gain access to the airway that supplant some of the need to wait for those kinds of phenomena, and that the issue about whether the patient wakes up to the point of being able to breathe on their own is dependent on the other agents that

are given during that process, as they are with this particular agent. You know, everything else being equal, reversing this more quickly might be of some advantage.

With regards to understanding how to proceed with this, I think it was pretty clear that succinylcholine is still a necessary part of the armamentarium and whether you would decide to use the sucs or the combination of rocuronium and the reversing agent will be a little bit up to what the anesthesiologist feels is most appropriate for the patient.

Clearly, in settings where we don=t know what the right dose is, as in obstetrics or where there is a potential contraindication as in renal failure, there is still a need to maintain and use the current therapies.

Have I understood that correctly? Does somebody want to add anything else?

DR. PROUGH: There was certainly a lot of appropriate discussion about exceptions to when you really couldn=t use this as an alternative to the succinylcholine. But I think, in fact, in the vast majority of circumstances if sugammadex were available you would, in fact, choose it as an alternative to succinylcholine.

I think there would be some exceptions and some additional data might be necessary to support the exceptions but my guess would be that at least 80 or 90 percent of the time you might be more comfortable starting off with rocuronium for induction rather than succinylcholine, knowing that if you had to reverse it you could reverse it.

DR. EISENACH: I am just curious whether the word Aimmediate@ means something special to the FDA because I don=t think five minutes or ten minutes is immediate in that situation.

DR. RAPPAPORT: Well, it was the applicant=s choice. We tend to stay away from those types of terms because the next product that comes in may be, you know, a minute or two more effective and wants to be ultra-immediate.

DR. SIMONE: The three minutes was based on a recommendation from the FDA, that at that point rocuronium has achieved its maximum effect. The thinking was that if you reverse it at that point you could probably reverse it at any point.

DR. EISENACH: Yes. No, I was just referring to the adjective of immediate reversal.

DR. SIMONE: That is a tougher one.

DR. FARRAR: I think that was a very useful discussion. What I would like to propose is that we take a short biologic break and come back in 15 minutes, so 3:05, please.

[Brief recess]

DR. FARRAR: We are moving on now to question number two. Question number two states, based on the nonclinical data submitted by the applicant from the sugammadex distribution, juvenile animal, reproductive toxicology, and dedicated bone studies, (a), has the risk for adult patients, including patients with fractures or surgical injury to bone been adequately characterized?

(b), has the risk for pediatric patients been adequately characterized?

(c), does the nonclinical data support the safety of sugammadex for clinical trials in a pediatric population?

(d), if the answers to any of the questions above is no, what additional information is required to support the use of sugammadex in these populations?

So, understanding that (d) applies to (a), (b) and (c), let=s start with (a). Has the risk for adult patients,

including patients with fractures or surgical injury to bone been adequately characterized? Thoughts?

DR. PROUGH: I think that the risk to patients with fractures or orthopedic surgery is adequately characterized. I think it appears to me that the margin of safety is likely to be quite large.

DR. SORIANO: Just to echo some of my pediatric colleagues here, as far as number 2(b), has the risk of pediatric patients been adequately characterized, it seems as though they have done a lot of histological studies but the functional studies haven=t been borne out yet. The load-bearing I think you mentioned haven=t been done yet.

DR. FARRAR: I agree we need to discuss the pediatric issue but let=s just be clear that in adult patientsB-I guess the real question here is do we feel like we have adequate information to say that a patient with a broken hip who is going to need bone repair in order to recover will not be adversely affected by using this drug, and are we comfortable with that.

DR. DESHPANDE: Just a point of clarification on your question, this is the adult patient that is not OB and not the special population that were excluded from this?

DR. FARRAR: We are addressing here the issue of bone-related issues, not the other comorbidities that we were discussing before. Yes?

DR. NUSSMEIER: I would say yes, with postmarketing surveillance monitored.

DR. EISENACH: Well, I think it is interesting to use a developing fetus as a model for fracture regeneration. I agree that some of the processes are similar, and the processes later in biology are similar to what happens embryologically frequently but they are not the same. They are similar but not the same. Some of the processes are regulated quite differently.

It depends on what you mean by Aadequately@ here. Is it adequate to have a label that has no mention of a concern? I think without at least some preclinical data in a fracture model--and a potential concern although at very high doses, I agree with Don that the margin of safety here is pretty highB-I think it would deserve a comment in the label.

I don=t think it deserves any sort of strong negative wording within the label against its use there. But I don=t think we know because I think, as Dr. Monk said,

although there were orthopedic patients the studies weren=t really designed to look at healing parameters over the long term with them. That is my opinion.

DR. FARRAR: Any other comments about adults, otherwise let=s move to the pediatric population. Dr. Soriano, you started us off.

DR. SORIANO: Yes, I just want to reemphasize that I don=t think the studies are complete until you get the functional studies in the juvenile rat model reported. After all, you can have histology but if function is somewhat disturbed you will definitely see a clinical marker.

DR. FARRAR: So, let me ask you directly, do you think that there is enough data to justify the safety from the perspective of moving ahead with a pediatric trial?

DR. SORIANO: No.

DR. FARRAR: What would you recommend specifically?

DR. SORIANO: Well, completing the studies. Well, there is still a question out there. Let me restate my observation. From what I understand from the presentation, they have provided real elegant histological studies in the juvenile rat model. The adult model is complete. The young

rat model is complete. But for the juvenile rat model there are still a couple more things they need to report. That is, functional studies, the load-bearing studies, what other studies they have using the fracture model they have on the femur, to have that complete in the juvenile rat model.

DR. VAN DEN DOBBELSTEEN: Can we clarify?

DR. SORIANo: Sure, if the rule allow it.

DR. VAN DEN DOBBELSTEEN: Diels van Den Dobbelsteen, toxicology. We have certainly been considering bone strength measurements in the juvenile rat models as well. But, as you may remember from the slides, there was impaired femur length or lower femur length due to the general toxicity of the compound. Now, typically in those kinds of situations where you have different bone dimensions you inherently get an effect on bone strength just because of the size of the femur, which is put into strength measurement apparatuses, will give you different results but it would be clinically not meaningful.

Therefore, we have limited ourselves to micro-CT measurements and Prof. Genant is much more appropriate to talk about the relation between femur strength and the micro-CT measurements that you can do. Please come forward

and address this gentleman=s concern, please.

DR. FARRAR: Excuse me, could you just wait one second. Do you need more clarification?

DR. SORIANO: Yes, I would like to know.

DR. FARRAR: Okay.

DR. GENANT: Well, as I indicated before, in the adult rat and in the young rat models we have the preclinical data that are strongly supportive of the absence of a negative effect on BMD, on the BVTV, the various parameters, as well as on strength parameters. In the juvenile model the results are somewhat mixed. That is, several of the parameters show a slight positive effect of the drug, marginally significant, and one of the measures, which is the nano-indentation, shows a slight negative effect at three weeks but that is reversed by the sixth week.

On the balance, these effects on the skeleton are very modest, either positive or negative. So, we are not seeing a substantial toxic effect that should be of concern with regard to fracture healing.

Another parameter that one can look to see if there is a substantial bone effect is the change in the

biomarkers and there were no significant changes in the biomarkers. So, that also is reassuring. Because in all of the osteoporotic drugs and the various antiresorbers or bone formers, there are always substantial biomarker effects. We don=t see that with this drug.

DR. SORIANO: Thank you.

DR. DESHPANDE: We have kept our focus at the moment on impact on bone. The other question for me in the developing organism, in the developing human is that this medication, once approved, will be at least available for use, not necessarily approved for use, in infants and children. And, the question that I would ask the rest of the colleagues on the committee is do we have enough information from a pediatric standpoint about the impact on endogenous steroids and hormones, particularly because most of the children=s hospitals see patients who come back for repeat operations? So, if that is part of the question, then I haven=t seen those data.

DR. EISENACH: If the question relates to can they do clinical trials in kids, I think your point is valid that if they are going to study repeated exposures in kids that might be problematic with the data that they have. If the

are going to do what they have done in adults with single exposure, do you feel comfortable with single exposure type studies?

DR. Deshpande: I don=t know. I would have to ask Sul and David. I am a little nervous about saying it is okay for single exposure, principally because I don=t have enough information to say that it is safe even for that single exposure, and knowing that from the clinician=s standpoint the single aspect is really not kept in mind when the drug is available for the patient.

DR. NICHOLS: I guess my opinion on balance would be that it is okay to proceed with studies on single exposure. I do support Sul=s desire for more functional studies on bone and enamel but, you know, there are a lot of promising features with this drug, and I think the one study that we briefly saw reflecting the pediatric population did seem to give some comfort that one could do a study safely in this population with single exposure.

DR. SORIANO: Another issue along the lines of pediatrics is the use of this drug in the immature neonate or the premature neonate. As many of you know, the renal function is somewhat impaired as well at that age, and

whether or not the dosing regimens that you will be looking at will actually become somewhat toxic for clinical use-BI mean, the recommendations for dosing may be toxic in these neonates and need to be studied, need to be borne out. And, I didn=t see any preclinical studies looking at the immature renal system and the effect of this drug as far as clearance and those other parameters. Do you have a response to that or did I miss something in your presentation?

DR. VAN DEN DOBBELSTEEN: With regard to the rat model renal system, as the animals are born the renal system is actually quite well developed so the developmental toxicity towards the renal system has been studied basically in our embryofetal development studies where kidney development goes on. And, neither in the embryofetal development study in the rat nor in the rabbit nor in our pre- and postnatal study did we see impairment of renal function in either the rat embryos or in rats going off with their mother for another eight weeks after birth. So, in that respect we don=t expect any untoward effect on the developing renal system.

DR. SORIANO: So, this illustrates the fact that there is interspecies variability. Certainly in the

neonates I take care of, the premature neonates especially, they have impaired renal clearance and this may be an issue that you may have to confront when you look at this drug and its use in pediatric patients.

DR. FARRAR: So, to summarize, my understanding of what has been discussed so far is that with regards to the risk in the adult patient we don=t have any evidence either for or against there being a problem here. The suggestion is that there is clearly no evidence to suggest that there is a problem but, given the potential for sequestration that was seen in young animals and the potential that that might also occur in fracture models, that there be some observation of this postmarketing if the drug were to be approved, and that would be the only suggestion with regards to that.

The second issue which comes up with regards to the pediatric population is that there could be some additional studies. Again, it would perhaps be useful to look at a bone fracture study in an animal setting to see whether there is increased uptake in that setting.

With regards to is the risk for the pediatric population adequately characterized, I think from what I am

hearing it has not been adequately characterized; that there are still some additional pieces of information that are necessary. It sounds like that clearly in the planning that you are doing now there may well already be plans for some of these, or you may have completed some of them and haven=t reported them. But there is a need to be looking at the data, especially with repeated exposures in these groups, to understand not simply the single curve washout in 172 days but to understand what would happen if pediatric patients were to get them with some regularity over the course of their stay, and whether that would ultimately lead to a level that would be a significant problem.

Then the issue with regards to the renal system in very young or premature infants. There has been some suggestion that it is different in humans than in rats and rabbits, and it suggests that there needs to be some further look at that. I am not knowledgeable enough to know what that should be exactly but clearly it is something to consider.

In terms of the nonclinical data supporting a clinical trial in the pediatric population, what I heard was that certainly single exposure seems to be adequate data to

suggest that those kinds of trials would be reasonably safe, but that there is clear concern about making sure that all the i=s are dotted and the t=s are crossed with regards to the animal studies before proceeding with those, and not proceeding to multi-dose studies in kids until those things have been carefully studied in animal models.

Did I get everybody=s point? Moving on then to question three, and this will be a voting question, there are three parts to it. The third one was added this morning so it may not be on your handout. You can read it up on the screen here.

The question goes has the applicant adequately demonstrated that sugammadex, (a), reverses neuromuscular blockade from rocuronium and vecuronium? (b), immediately reversesB-and I think we can change that word perhaps but immediately reverses neuromuscular blockade from rocuronium? And, (c) can be safely used in the targeted population, specifically with discussion about the potential hypersensitivities in this population and how that might apply if patients at risk cannot be identified a priori?

I think we want to take these separately and we can start with the easy one first. Does the group as a

whole believe that adequate data has been presented about the reversal of neuromuscular blockade from these two agents? Unless anybody feels pressed to discuss it more, I think we could probably go right to the vote. Is that okay? According to Mimi, you need to raise your hand and then you need to speak into the microphone. So, I need a show of hands for yes and when you speak into the microphone you need to say your name and your vote. Okay? So, all those who think there is adequate data?

[Show of hands]

DR. SORIANO: Sul Soriano, yes.

MS. ARONSON: Diane Aronson, yes.

DR. EISENACH: James Eisenach, yes.

DR. FARRAR: John Farrar, yes.

DR. POLLOCK: Julia Pollock, yes.

DR. ZELTERMAN: Dan Zelterman, yes.

DR. NUSSMEIER: Nancy Nussmeier, yes.

DR. DESHPANDE: Jay Deshpande, yes.

DR. NICHOLS: David Nichols, yes.

DR. PROUGH: Don Prough, yes.

DR. PHAN: We have ten yes, zero no and no abstained.

DR. FARRAR: For the second question, assuming that the word Aimmediate@ gets changed to something like rapidly or a word choice of the agency=s preference, the question I think addresses whether sugammadex reverses neuromuscular blockade from rocuronium--

DR. EISENACH: [Not at microphone; inaudible].

DR. FARRAR: But the issue is immediately. Does it meet the criteria for use in an urgent situation? That was the discussion that we had fairly extensively and I think the purpose, if I understand the question correctly, is, you know, do we feel there is enough data to support its use in that circumstance as being at least as good as or better than current therapies that are available, current treatments, in an urgent situation. Am I getting the question right? So, is there anybody that wants to say anything else about that?

DR. NICHOLS: It might be helpful, if the modifier Aimmediately@ is not going to be used, if we were clear on what modifier is to be used here.

DR. RAPPAPORT: I am not sure we can come up with that sitting here at the table today, unfortunately. We will probably work with the sponsor to come up with some

more appropriate wording to address this. What we are trying to avoid is an emerging war of terminology with various companies. We will get the concept in there. This is sort of what we do for a living. This is a lot of wordsmithing so we will come up with the right wording to address the issue without using Aimmediately.@

DR. FARRAR: Does that help you?

DR. DESHPANDE: So for a forma vote we are just going to put Aimmediately@ in parentheses or quotes or something?

DR. FARRAR: We will leave Aimmediately@ in. I mean, I think the real question here is whether there is enough data from what has been presented for this to have an indication for use in the emergency situation that you face where you have to do something urgently and potentially reverse that. I am struck by the cases that Dr. Eisenach has with regards to encountering a difficult airway that you didn=t expect to be difficult in the pregnant population, and other circumstances, morbidly obese, whatever the circumstances are. And, I think the real question here is whether there is something special about this particular combination that would lead you to feel that should be

specifically indicated for that.

DR. ROSEBRAUGH: I think everybody is going to get hung up on the Aimmediate@ and really what I think the team is interested in knowing for the purpose of labeling is its use clinically relevant in an urgent situation? Is that sort of what you are trying to get at? Would that be an easier question for you folks to approach than trying to figure out what Aimmediately@ means? Because that is sort of what we want to know.

DR. FARRAR: Are people more comfortable with that?

DR. NUSSMEIER: The other part that is not clear to me is, as we vote on this question regardless of what happens with the wording Aimmediately,@ are we also voting on subsequent sentences that have to do with the scenario or the emergency or Acannot intubate/cannot ventilate@ or any other scenario? Are we only voting on this sentence as written with parentheses around Aimmediately?@ Because there really are differences between efficacy for reversal, profound neuromuscular blockade and the next leap to a whole set of scenarios.

DR. ROSEBRAUGH: Well, I think that is really what we are trying to get at, whether you can make that leap to

that next set of scenarios based on what they presented.

DR. NUSSMEIER: That is a harder question.

DR. RAPPAPORT: What happens is that with that indication the implication is that you can use it for all those other settings. So, if we don=t think it is appropriate to use them for all those settings we will come up with terminology which states where it can be used, but we are trying to get a sense from you whether or not it can be used in those emergent settings.

DR. NICHOLS: So, if I were to vote yes on this sentence what I mean by voting yes would be that it reverses deep neuromuscular blockade quickly, very quickly, faster than succinylcholine will dissipate, and it does so in most people but not all. The data presented today do not test adequately, in my view, the emergency situation. There is no clinical model that is ethically defensible to do that and, as I said a couple of times, I think the issue for me is, is the patient exchanging gas spontaneously after giving this drug and I have not seen data on that.

DR. ROSEBRAUGH: Yes, I don=t even know that we need to vote, but what we really would like to hear is everybody=s view, just like what you just articulated.

DR. RAPPAPORT: But before we go on can I just get some clarification, Dr. Nichols? You say that you don=t think it has been adequately studied but then you also said that ethically you don=t think it can be studied. So, have they done as much as they possibly could here?

DR. NICHOLS: Well, I think they could present data on whether spontaneous ventilation is adequate after administration of this drug, and how soon after administration of this drug spontaneous ventilation becomes adequate. You know, a patient under one MAC of anesthesia for most anesthetics will breathe spontaneously. What prevents that from happening in the clinical scenario is the addition of neuromuscular blockade. So, I want to know if you take the neuromuscular blockade out at time zero how long from that time zero does it take for them to be able to breathe adequately enough to have a reasonable oxygen saturation.

DR. DESHPANDE: I would just like to echo that because I think this side of the table over here is hung up on the fact that we are assuming that this line really means that the approval applies to the Acannot intubate/cannot ventilate@ scenario. But the proof of that is actual

patient ventilation and, as Dr. Eisenach found out in his patients, sucs reversed and wore off and the patient started breathing. We don=t have data to date, or I haven=t seen data to date that says that that corollary applies in this situation.

DR. FARRAR: Dr. Prough?

DR. PROUGH: Even though I am on this side of the table, it seems to me that if you stick with the sentence regarding indications, leaving out for the moment the fact that the word Aimmediate@ is controversial, there doesn=t seem to be much question in my mind at all about the fact that the evidence strongly supports that indication. I think in the presentation that Dr. Shibuya made it is pretty obvious that some of the extrapolations aren=t warranted because there is not any data to address them.

In fact, what individual clinicians will do is incorporate this, until somebody standardizes it in a fairly individualized protocol with how to deal with an awful situation. But in situations where the clinician thinks that they have to make the rocuronium effect go away as fast as they possibly can it is indicated. I think you really run into trouble if you try to talk about what those

circumstances might be because they weren=t studied. In fact though, you can give rocuronium and reverse it relatively quickly, and many people probably would do that if they were in one of those emergency situations. But it seems to me we really get pretty far afield if we get too far away from the proposed indication.

DR. FARRAR: If I could sort of rephrase this a bit, what I think, if I understand Curt Rosebraugh=s point, is that the question that is being asked is in a situation where you are faced with a patient in whom there is at least the possibility that you would have to do an urgent reversal would this combination, and it really is a combination of these two agentsB-is there enough evidence presented here today to suggest that that would be a medically indicated, supported with evidence choice that you would make? I think that may be a question that we can either present comments on or vote. I would need to know from the FDA what you would like.

DR. RAPPAPORT: I think that is correct, and we are hearing the type of information we need to hear about this, and I would like to hear more about it if there is more discussion necessary. Then I would like a vote on whether

that information is available to support this or whether we need further data. I am hearing a little disagreement there. And, try to think of this as just responding to the question about the clinical setting and forget that question specifically up there because we will manage to find the right place and way to put this in the label so that it is clear to practitioners what we know and what we don=t know. What we want to know from you is should they be using it in that setting.

DR. FARRAR: If what I am hearing is correct, then what we are focused on here is when you have a patient in whom it may be necessary to do an urgent reversal for whatever the reason, is the combination of rocuronium followed by sugammadexB-is there enough evidence to support the use of that agent in that situation? That is what Bob I think is asking more discussion about. In that setting your answer is?

DR. DESHPANDE: My answer is yes in the population we have already talked about earlier.

DR. NUSSMEIER: Yes, my answer is yes, it is probably superior to succinylcholine in that setting, but extrapolating that to definitely avoiding a scenario whereby

there is hypoxemia would be too great a leap.

DR. POLLOCK: I agree with what Nancy said. Also, I think one of the things I am kind of hung up on is that I do really want to make sure that clinicians recognize it is not immediate in some patients. So, if you are counting on this to get you out of trouble in all patients, that may not be a smart thing to do.

DR. SORIANO: Well, perhaps this statement should be somewhat rephrased in that you can say situations that are complicated by prolonged neuromuscular blockade. If that is the case, then my answer would be yes because, certainly, we have all identified confounding variable in this Acannot intubate/cannot ventilate@ situation. But I think the problem that we are addressing here is the complicating effect of prolonged neuromuscular blockade and I think this drug is indicated for that situation so, yes, for me.

DR. FARRAR: Diane?

MS. ARONSON: That was helpful as before I was ready to abstain because I am not a clinician. So, that was helpful.

DR. FARRAR: So you are not abstaining now or you

are?

MS. ARONSON: I could vote yes given that presentation. Yes.

DR. EISENACH: Well, I think Don is right that the indication as proposed by the sponsor says very specifically what they studied and what they observed, and I think as long as you don=t say succinylcholine is forever contraindicated for rapid sequence induction, I think that very nicely encapsulates a clinical scenario that is very real in our practice, three minutes after rapid sequence induction can this be reversed? So, I think as an indication it has been appropriately studied in the patients that they have chosen to study.

DR. NICHOLS: I too would vote yes and for the reasons that Nancy and Julia have articulated. But I want to I guess caution the agency how this difficult this wording is I think going to be because you have a scenario right now where anesthesiologists have a whole range of invasive options in their heads and things to do when an airway cannot be achieved and a patient cannot be ventilated, and what you don=t want to have is for clinicians to say, oh, I can give sugammadex and that is

going to solve all my problems if I get into this scenario and I do not have to prepare for everything, from LMA to tracheostomy or cardiopulmonary bypass, if you can=t achieve an airway. So, how you phrase this I think is going to be critical.

DR. FARRAR: I have two people still to hear from but just to comment that everybody=s comments on this particular question that have been made in the last round are being noted for the record. Dr. Prough, do you have any other thoughts?

DR. PROUGH: No.

DR. FARRAR: Okay. And Dr. Zelterman?

DR. ZELTERMAN: Yes, I would agree. I was thinking the language might be timely relevant. It is timely, which is not to say immediate but appropriate time, but relevant also to the circumstances. So, I am trying to sound bureaucratic. I vote yes.

DR. FARRAR: So, let me propose the following, which is that the wording would be has the applicant adequately demonstrated that sugammadex in combination with rocuronium is useful in situations that may lead to the need for urgent reversal.

DR. RAPPAPORT: I think at this point we have heard enough discussion and gotten enough input that we probably don=t need the vote on this one.

DR. FARRAR: I am just as happy. Thank you. The third issue to consider is can sugammadex be safely used in a targeted population with specific reference to the potential hypersensitivities in this population if the patients at risk cannot be identified? We had some discussion about this earlier and I want to know if there is any additional discussion. Yes?

DR. SIMONE: I would just like to bring up one point to consider. There are some drugs which have been indicated for potentially life-threatening conditions, some of the antibiotics in particular, where one episode of Steven-Johnson syndrome is enough to have the drug removed from the marketplace. There are other drugs more pertinent to anesthesia, something like rapalon which was associated with histamine release which led to bronchospasm in some patients and deaths and it too was removed from the market for safety considerations.

We have here a case of one patient who was clearly at a minimum allergic to sugammadex and it has been

demonstrated multiple times, with no predisposing factors that could be attributed to identify similar patients. So, I am trying to get a feel for where in this spectrum of things does that safety issue come to bear in terms of whether or not you would limit the use of sugammadex to certain patients or certain situations, or is it something to be expected with all drugs and should not be considered problematic, or is it something that needs to be investigated further? That sort of discussion would be most helpful.

DR. FARRAR: So, the question is direct. Is the data that has been presented for this drug something that you, as investigators or users of these kinds of drugs, would have expected to see or is there some reason for additional concern that ought to be either looked into more or otherwise considered by the agency? Yes?

MS. ARONSON: Would it be helpful to understand the definition of targeted population? Does that equal healthy? So, then are we excluding some of the populations that have been discussed?

DR. SIMONE: At this point the population would be adult patients following neuromuscular blockade with either

vecuronium or rocuronium bromide, with the limitation that for those with severe renal impairment the drug would not be recommended for use.

DR. NICHOLS: So, my answer to this question is yes. I think it can be used safely in the targeted population. The issue of postmarketing surveillance was raised previously and I think for a variety of reasons to include postmarketing surveillance would be a good idea.

DR. Deshpande: I concur. I think one other targeted population that is off the list is maternity patients, OB patients. So, we are talking about renal patients, pediatric and OB that are off the list.

DR. FARRAR: Until there are additional studies in that population.

DR. DESHPANDE: Right, until additional studies are done. Right.

DR. NUSSMEIER: I agree, yes, with postmarketing surveillance. Three thousand patients is great; three million would be better and I think that is what it is going to take. We won=t have the answer until we have large numbers of patients.

DR. ZELTERMAN: I agree. It is a very large

population. I think it was presented well.

DR. POLLOCK: I agree, yes.

DR. FARRAR: I agree, yes, with the stipulations previously made, the need for postmarketing surveillance.

DR. EISENACH: I have a problem with saying that this drug would be useful for unanticipated difficult intubations and then excluding it from the population that has the highest incidence of unanticipated difficult intubations. I understand that they would want to exclude pregnant patients. They haven=t studied them; it is appropriate for them to exclude them. It just bothers me that we are saying in essence, yes, this should be used for rapid sequence intubation but, no, it should not be used in a pregnant patient. That just bothers me as an obstetric anesthesiologist. So, it is kind of like having their cake and eating it too in a way, I guess that you get the rapid sequence indication which is, in essence, what that wording is in the unanticipated difficult intubation and you are missing that group.

So, clearly the targeted population, and there is no way around it, they have to do that. They have not studied pregnant patients. They can=t say anything about

it, other than it is unstudied and you may want to say something about doses may be greater, or something, but I think that is probably appropriate.

DR. FARRAR: I guess to follow up, you also brought up the fact that you wouldn=t use it currently in that population because you don=t know how much to use. So, if I am hearing you correctly, what you are suggesting is that they quickly go ahead and do those studies.

DR. EISENACH: They are hard studies to do, unfortunately, because general anesthesia in Cesarean section is used rarely in the United States. It is not uncommon in other countries so it could be done elsewhere but here it is not.

I guess when Vioxx had a little bit of a problem there was not a lot of preclinical data supporting the problem of cardiovascular toxicity with Cox-2 inhibitors. And, I don=t think there is any reason you would anticipate this kind of a drug would cause cardiovascular problems. The problem with Vioxx was something quite difference than acute dysrhythmias, of course, so we are talking about a whole another order of magnitude but the effect size I don=t think was that much different. So, you know, from looking

at the effect size of the cardiovascular data, it is almost double the placebo group. Again, with overlapping confidence intervals, it is probably just noise but you have a signal that is about double.

I think it would be appropriate to move ahead. I think the company really should look very carefully at postmarketing surveillance for cardiovascular events based on what I have seen today. But I think it is appropriate to move ahead.

MS. ARONSON: Can I humbly ask for a review on the pediatric population in relationship to this question and the neonatal population?

[Comment off microphone]

MS. ARONSON: I would say yes then.

DR. SORIANO: Yes.

DR. PROUGH: Yes.

DR. FARRAR: That wasn=t quite formal. Do you want formal or is that good enough? I am being told we should do it formally. Can everybody who just said, which I think was everybody, please raise your hand?

[Show of hands]

DR. SORIANO: Sul Soriano, yes.

MS. ARONSON: Diane Aronson, yes.

DR. EISENACH: James Eisenach, yes.

DR. FARRAR: John Farrar, yes.

DR. POLLOCK: Julia Pollock, yes.

DR. ZELTERMAN: Dan Zelterman, yes.

DR. NUSSMEIER: Nancy Nussmeier, yes.

DR. DESHPANDE: Jay Deshpande, yes.

DR. NICHOLS: David Nichols, yes.

DR. PROUGH: Don Prough, yes.

DR. PHAN: We have ten yes, zero no, zero abstain.

DR. ROSEBRAUGH: Can I just ask for a point of clarification because I think Dr. Simone asked a real specific question. Where do you see this falling between the two extremes when a drug is removed because you see something like anaphylactic reactions versus not? So, am I hearing from the committee that you guys are saying that even if the incidence was 1 in 2,000, which was their exposure, that doesn=t bother you?

DR. NICHOLS: Well, I will not sign off on nothing bothering me. What I will say is that I am impressed from the results we saw today that the events were mild and did

not require treatment, as I understood it, and that is playing into my decision making on the hypersensitivity. Frankly, I am much more concerned about the cardiac issues than I am about the hypersensitivity issues.

DR. NUSSMEIER: To specifically answer your question, if it turns out that 1 in 2,000 patients had severe needs to be treated, anaphylaxis, then no. You know, that would have a significant impact on the later marketing of the drug. But for the present we don=t have any data that that would occur.

DR. FARRAR: Anybody else want to enter a comment on that? I will admit to looking at the evidence that has been presented and the fact that the occurrence of events, except for this one, were almost equal in the two groups suggests that careful watching is probably appropriate. I think we have all commented here that the number of drugs that are given in the process of putting a patient to sleep for surgery or other procedures are numerous and to blame it on one of the drugs that is given only I think is probably premature given the data that is presented. The fact that the numbers are almost equivalent between the placebo group and the treated group is at least some evidence that the

drug may not be the primary cause, with the very big caveat that the placebo group was much, much smaller or substantially smaller than the treated group, at least as I understood the data. But that would be my only other addition.

DR. PROUGH: I think the 1 in 2,000 estimate, which certainly from these data is as high as the problem might be, also has to be looked at in the context of the alternatives. I don=t know how to put a number on the complication rate associated with succinylcholine but there certainly is one. And, if you decide that to avoid succinylcholine you are going to use non-depolarizing neuromuscular blockers, then you set yourself up for the occasional occurrence of not being able to intubate and ventilate the patient who has received a non-depolarizing neuromuscular blocker, and at least some of those cases will result in potential morbidity or mortality. So, I think even if this drug actually produced anaphylaxis that required treatment one in 2,000 times I might still be inclined to think that it is better than the alternatives.

DR. FARRAR: Did that get to your point?

DR. ROSEBRAUGH: Yes.

DR. FARRAR: So, let me ask our colleagues from the FDA whether there is any other information that you would want from this august body of anesthesia and one neurologist experts and statistician.

DR. SIMONE: I think your comments were very helpful in helping us proceed. As has been mentioned multiple times, our reviews are still ongoing so our findings are subject to possible changes as the data is more fully analyzed. But your input has given us some parameters within which to look at the indications and the risk factors involved. Thank you.

DR. RAPPAPORT: Yes, I just want to echo Art=s comment that this has been enormously helpful to us today. These meetings can sometimes not provide a lot of help but this one was particularly helpful so I want to thank you all for your comments.

DR. FARRAR: Let me add my thanks as the chair for everybody=s cooperation and I very much appreciate everyone taking the time to come and be here. I am glad to give you a little gift in that we are ending just a tad early and so maybe we will actually make those trains, planes and buses. Thank you very much.

[Whereupon, at 4:00 p.m. the proceedings were adjourned]