mg/kg and a re-administration dose of 1.2 mg/kg rocuronium is attempted, then there is no waiting time required. However, if a lower dose of rocuronium is going to be applied, then the waiting time of six hours needs to be applied, and so on and so on. Is that clear?

DR. DESHPANDE: Thank you. My other question was age and the human equivalent of the juvenile rat model that you are using because there was a comment in your presentation about pediatric concerns. So, for the adult rat model and the juvenile rat model where would you equate that to the human population?

DR. BOEN: I would have to refer that question to Dr. van Den Dobbelsteen.

DR. VAN DEN DOBBELSTEEN: I understand you are specifically interested in the relative bone age. Right? As you might know, the rat is a species which contains an epiphyseal disc that is different from man. The epiphyseal disc would typically close between the age of 12 and 18 years. So, basically the juvenile model is very comparable in that sense. The age range that we studied was up to 7 days old, 14 days old, 21 days old and the ones that were 7 days old have also been dosed for 4 weeks. So, that

basically is comparable in bone age as compared to man.

DR. FARRAR: Dr. Pollock?

DR. POLLOCK: I would like to follow up for just a minute on the use of succinylcholine added to the use of sugammadex. In some of your background material you indicated that in that instance the duration of succinylcholine would be prolonged. My question is when is that correct and, second, is there any change in the onset? If that is correct, why would that be? And, two, is there any change in the onset time of succinylcholine if it is used after sugammadex?

DR. BOEN: That is actually true, but the one who is best equipped to explain that would be Dr. Ton Bom.

DR. BOM: We have indeed investigated how we could address this issue. Can I have the slide on, please?

[Slide]

These results were actually presented at the last ASA meeting. We see here the time to 90 percent blockade and time to maximum blockade for saline-treated animals which just received succinylcholine. We see very fast onset so you get complete block within one minute. When we give first rocuronium and obtain complete block and then reverse

it with a dose just enough to get complete reversal, we see that the subsequent administration of succinylcholine gives delayed onset of block. However, when you give rocuronium first, the normal dose for guinea pigs of 0.5 Φg/kg sugammadex, you have complete reversal and then you administer 1.5 Φg/kg sugammadex and then you inject succinylcholine again you get the same normal onset time.

As an easy way to explain this, to get complete reversal you don=t have to encapsulate all the rocuronium. Only 30 percent of the post junction receptors have to be available to succinylcholine to get complete reversal. When you then administer sugammadex 70 percent of the receptors are potentially still paralyzed or occupied by rocuronium. That means that they cannot be depolarized by succinylcholine.

Once we give a much higher dose of sugammadex and all these receptors have been liberated from the occupation of rocuronium, they can all be depolarized again. So, in patients with sugammadex, or in this case just guinea pigs, in guinea pigs you can get really fast onset again once you liberate all the receptors from rocuronium and allow succinylcholine to depolarize all these receptors.

DR. POLLOCK: I had another question. So, clinically would that mean that if I need to re-intubate somebody in a hurry I should give a second dose of sugammadex--

DR. BOM: A second dose of sugammadex. Yes, I would recommend that.

DR. FARRAR: Dr. Soriano?

DR. SORIANO: Yes, this is a follow-up question to Dr. Nussmeier=s concerns about the renal effects or problems of renal function. In your studies in elderly, and I imagine in Dr. Monk=s studies, you used a dose of 2 mg/kg. Looking at the molecular structure of the complex of stuff, these are large molecules and I wonder if anyone has done studies looking at the effect of these large molecules on renal function, perhaps leading to acute tubular necrosis in the laboratory animal for instance.

Giving a huge load, 16 mg and up per kilo, does that affect renal function or produce acute tubular necrosis in those high doses? Certainly, elderly patients may have some marginal renal function as well, so if you start moving up to those higher doses perhaps you may start seeing some morbidity associated with the use of this drug.

DR. BOEN: Thank you. I would like to refer this question to Diels van Den Dobbelsteen.

DR. VAN DEN DOBBELSTEEN: Slide on, please.

[Slide]

In this slide you will see the safety margins we have established in the rat and the dog four-week toxicity studies. We have basically been looking at it histopathologically. Now, the typical effects you see of cyclodextrins is, first, adaptive responses showing histopathological changes but initially certainly not associated with pathology, and also not showing progressive pathology if you would have prolonged exposure.

So, the note shows that there is an effect level in rat, which is a very sensitive species because of its high glomerular filtration rate. You can see even up to a dose of 16 mg/kg a safety margin. Actually, it is the maximum dose we have been able to put in the animal and it even gives you a safety margin of 22.2. Does this sufficiently address your question? Thank you.

DR. FARRAR: Are there other questions? I have one last question, if I might. Cyclodextrins, as was implied, have been used for a number of other uses and I wonder

whether the sequestration in bone has been studied in any of the other similar types of compounds.

DR. BOEN: Good questions. I will have to ask Dr. van Den Dobbelsteen again to come back to the microphone.

DR. VAN DEN DOBBELSTEEN: Well, let=s not make it a one-man show, right? From all the public data on other cyclodextrins I am not aware that they bind to bone. So, it has not been publicly revealed if it were to.

But, again, the agencies that must have studied the files for excipients, hydroxypropyl beta cyclodextrin or sulfobutyl ether beta cyclodextrin, and so forth, could be able to answer that. I just don=t know. I have not recovered any literature reports on it. So, it might be specific to sugammadex; it might not be. But typically the doses of these excipients are, like, 10-30-fold higher in multiple dose regimens so that also has to be taken into account.

DR. FARRAR: Any additional questions?

DR. EISENACH: I have one real quick one.

DR. FARRAR: Sure.

DR. EISENACH: Just one quick question about the second indication in reversal of dense block in a failure to

intubate/failure to ventilate situation. Have you looked at this drug in a large number of obese patients or in any pregnant patients where these kinds of situations occur?

DR. BOEN: You mean the immediate reversal, right?

DR. EISENACH: Yes, I am talking about reversal in a failure to intubate scenario that you are trying to mimic in your clinical trials.

DR. BOEN: Right. Fortunately, we also have an investigator from that study here. That is Dr. Scott Groudine. So, he may be able to provide us with some information on this.

DR. EISENACH: The question was pregnant patients and obese patients.

DR. GROUDINE: There were no patients who were either obese or pregnant.

DR. FARRAR: We will proceed to break for 15 minutes. We should return and restart at 11 o=clock. I am sorry, one last thing, if the members of the committee could look in their packet and fill out their lunch menu and return it to Mimi Phan? Thank you.

[Brief recess]

DR. FARRAR: The second half of the presentations

is the FDA presentations. We will have questions for this after lunch. So, please, if the members of the committee could write down their questions so that we can remember them through lunch. The first is Dr. Shibuya.

FDA Presentations

Sugammadex: Efficacy and Outlier Analysis

DR. SHIBUYA: Good morning.

[Slide 1]

My name is Rob Shibuya. I am a medical officer in the Division of Anesthesia, Analgesia and Rheumatology Products at CDER. I am responsible for reviewing the efficacy portion of this application. Dr. Arthur Simone, from whom you will hear shortly, is conducting the safety review. Currently our review is ongoing. Since our review is not complete we are presenting our findings as preliminary.

[Slide 2]

My presentation will cover the indications proposed by the applicant. We are reviewing the appropriateness of the proposed indications and I will refer to the conditions tested in clinical trials as scenarios. I will briefly cover the development program focusing on the

Phase III studies.

I will very briefly discuss two similar studies, studies 301 and 302, since the applicant has presented these studies in detail previously. I will spend more time discussing study 303. Last, I will present our preliminary conclusions regarding efficacy.

[Slide 3]

In this slide I have copied the proposed indications and usage from the applicant=s packaged insert, which I will read: Routine reversal: Sugammadex sodium is indicated for routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium.

The second indication reads: Immediate reversal: Sugammadex sodium injection is indicated for immediate reversal of neuromuscular blockade at three minutes after administration of rocuronium.

[Slide 4]

While the applicant has conducted a complete clinical development program consisting of the usual Phase I, II and III studies, I will limit my discussion to the pivotal studies. The applicant has described study 301 and 302 and I will say nothing more about them at this point.

Study 303, used to support one of the proposed indications, investigated sugammadex in a specific scenario with a different comparator. I will cover this separately later.

[Slide 5]

We will skip this slide. It was well covered by the applicant.

[Slide 6]

This slide summarizes the results from study 301 and 302. I have shown the sample sizes, the scenarios tested, the summary statistics for the primary efficacy endpoint by treatment group and the p value.

As you can see, sugammadex was more effective than the comparator, with p values less than 0.0001 for all comparisons. When you compare the data when patients were blocked with rocuronium versus vecuronium the data suggest that the drug is more effective with rocuronium, although we note that the studies were not designed to inform this.

[Slide 7]

The statistical analysis plan focused on a comparison of means which I have shown you in the previous slide. When data for individual patients were examined, not unexpectedly, some patients were outliers, meaning that

sugammadex was less effective than what would be expected.

To visually depict this I have plotted the endpoint data, time from sugammadex injection to the T_4/T_1 ratio of 0.9, as a Kaplan-Meier type analysis. Patients treated with both rocuronium and vecuronium were pooled here and for all these other slides. Time to endpoint in seconds is on the abscissa and the proportion of patients meeting endpoint criteria are plotted on the ordinate.

We can see that the large majority of patients endpointed very rapidly, consistent with the mean between 90 and 150 seconds that I showed earlier. However, circled in red, we see that not all patients responded to sugammadex as well as the majority of patients. In particular, the time to endpoint for this patient exceeded 64 minutes. In the analysis using the comparison of means these outliers are unapparent.

[Slide 8]

This slide is the identical analysis for study 302, the so-called profound block study. Again, most of the patients responded rapidly, consistent with the mean of 3.0 to 4.5 seconds, which is 180 to 270 seconds. I draw your attention to these two patients who took more than 47

minutes and more than 63 minutes to reverse.

[Slide 9]

Now I will shift my focus to study 303. The overall design, a randomized, safety assessor-blinded, active-controlled study is the same as the other pivotal studies. This study enrolled only category ASA 1 and 2 patients. There were two treatment arms. Half the patients received rocuronium, dosed higher than the other studies, at 1.2 mg/kg that was followed with a high dose of sugammadex, 16 mg/kg.

The other half of the patients received succinylcholine dosed at 1 mg/kg. Again, patients were monitored for neuromuscular function. Since succinylcholine does not cause fade, the endpoint selected was time from the NMBA administration to the point where T_1 returned to 0.1.

[Slide 10]

I have copied the table showing the statistical summary for the primary efficacy endpoint for study 103 from the NDA submission here. To clarify, in this table the applicant uses Org 25969 to reference sugammadex, the investigational product.

We see that 55 patients were treated in each arm.

The applicant used a conservative imputation method and proposed to use the analysis with imputed data for the primary analysis.

So, I draw your attention to the data in the top half of the table. We can see that there was a difference in the mean elapsed time from the time of NMBA administration to the return of the T_1 to 10 percent. It was 4 minutes and 22 seconds in the rocuronium plus sugammadex group versus 7 minutes and 4 seconds in the patients who were treated with succinylcholine and allowed to spontaneously recover. This difference was statistically significant.

[Slide 11]

To put the next two slides in the context I will revisit the slide that I already showed you showing the applicant=s proposed indications. I am going to go ahead and read the highlighted text: Immediate reversal: Sugammadex sodium injection is indicated for immediate reversal of neuromuscular blockade at three minutes after administration of rocuronium.

[Slide 12]

I wish to draw the committee=s attention to some

language from a section of the NDA entitle clinical overview. I will read pertinent excerpts from that document.

The document reads: Org 25969 will allow for easier management of the Acannot intubate/cannot ventilate,@ CICV, scenario. As a result, use of Org 25969 in a CICV situation following rocuronium administration may prevent the need for emergency noninvasive airway ventilation including rigid bronchoscopy, combitube ventilation, or transtracheal jet ventilation, and may prevent the need for emergency invasive airway access such as surgical or percutaneous tracheostomy or cricothyrotomy.

[Slide 13]

To continue, the clinical overview states, as described above, the results from trial 19.4.202 support the conclusion that replacement of succinylcholine with a combination of rocuronium followed by Org 25969 to reverse the neuromuscular blockade would potentially markedly reduce the morbidity and mortality caused by a CICV scenario.

[Slide 14]

Regarding the sugammadex development program, including study 303 and the language in the clinical

overview, we note the following: Number one, sugammadex was not tested in the CICV or emergency scenario and, number two, the statements in the clinical overview do not address other reasons for apnea such as the drugs used for induction.

As we have seen in the clinical overview, the applicant proposes that sugammadex would be useful in a Acannot intubate/cannot ventilate@ scenario, a medical emergency. As noted in this slide, the language in the clinical overview does not account for the effects of the induction drugs. So, in the context of the applicant=s proposal and the outliers that we observed in studies 301 and 302, let us reexamine the data from study 303.

[Slide 15]

The mean time from the injection of sugammadex to return of T_1 to 10 percent was 4 minutes and 22 seconds in study 303. However, 3 minutes of those 4 minutes and 22 seconds are due to the artificial situation mandated by the protocol designed to permit the rocuronium to reach maximal effect. In practice it is difficult to know when the clinician might elect to use sugammadex. Therefore, we conducted an analysis of the time from the injection of

sugammadex to various endpoints.

This figure shows a Kaplan-Meier analysis. This is the time from injection of sugammadex to the primary endpoint, T_1 equals 0.1. In this case it is not in seconds, it is in minutes and seconds, again, minutes and seconds here in proportion to patients endpointing.

I have also provided a table. I chose the number of patients who endpointed in less than 1 minute, 1-2 minutes, 2-3 minutes and more than 3 minutes. You can see that 91 percent of the patients reached T_1 equals 0.1 within 2 minutes, although one patient required over 3 minutes to reach endpoint from the time of injection of sugammadex. Depending on how one defines Aimmediate@ we note that even the patient who responded the most quickly still required 29 seconds to reach endpoint.

The endpoint of the T_4/T_1 ratio equals 0.9 is generally recognized as clinically significant. Let us look at the same analysis to that endpoint.

[Slide 16]

Again, these data are measured from the time of sugammadex injection, presumably the time that the anesthesiologist decides that reversal of neuromuscular

blockade will benefit the patient.

When we look at the clinically relevant endpoint of T_4/T_1 equals 0.9 we see that only 61 percent of patients reversed in less than 2 minutes; 13 percent, down here, took longer than 3 minutes to reverse; and one patient took over 14 minutes to reverse. If the clinician were depending on sugammadex to save this patient=s life in all likelihood the outcome would not have been favorable.

[Slide 17]

This slide shows the same analysis applied to one of the secondary endpoints, T_1 equals 0.9. These data show that 32 percent of the patients required more than 3 minutes to reverse, with 4 percent or 2 patients requiring more than 7 minutes.

[Slide 18]

In summary, our preliminary efficacy findings are that study 301 showed that sugammadex is effective in the routine, shallow scenario. Study 302 showed that sugammadex is effective in the routine profound scenario. The extrapolation of the results of study 303 to an emergency or CICV situation is not supported.

This concludes my presentation and I would like to

invite Dr. Simone to the podium.

Sugammadex: Safety Considerations

DR. SIMONE: Good morning.

[Slide 1]

I am Arthur Simone. I am a medical officer on the anesthesia team in the Division of Anesthesia, Analgesia and Rheumatology Products, and I have been charged with conducting the primary review of the clinical safety data related to the administration of sugammadex.

[Slide 2]

It should be noted that the safety review is ongoing and that the presentation to follow is based on preliminary findings.

[Slide 3]

The safety database submitted by the applicant was derived from 28 clinical trials in which 1,973 adults were exposed to sugammadex. All but 128 of these individuals were exposed to sugammadex following the administration of a neuromuscular blocking agent. The majority of the subjects were healthy individuals. Forty-one pediatric subjects, ranging in age from less than one year old to 17 years old, were also exposed to sugammadex in a European study that was

not conducted under the IND. The final study report of a hypersensitivity study, also conducted abroad and not under the IND, was submitted within the past two weeks.

[Slide 4]

Before focusing on safety findings let=s look first at exposure to sugammadex within the development program. In this table numbers of unique subjects and numbers of exposure for doses of sugammadex are listed as doses associated with serious adverse events and represents the number of unique subjects exposed to each of the doses, and these are the exposures. As an aside, the highest dose of sugammadex used in any trial was 96 mg/kg.

Included in this table are the comparators used in the clinical trials, specifically placebo, over here, and neostigmine. Although neostigmine is marketed in this country it has never been approved by the FDA for any indication yet it has long been the most popular agent for reversal of neuromuscular blockade.

The bottom two rows of the table present the number of serious adverse events, or SAEs, which were associated with each drug and each drug dose combination. The percentage of unique subjects who experienced a serious

adverse event for each of these categories is listed on the bottom row. Overall, there was no dose-dependent trend in the occurrence of serious adverse events and the percentages observed with sugammadex did not differ substantially from the higher doses of neostigmine.

[Slide 5]

Now let=s turn our attention to the preliminary safety findings. It should be noted that our findings to date have not been inconsistent with those of the applicant, however, our interpretation of the findings may be somewhat different. In our review thus far two specific areas of concern related to safety have been identified. These include electrocardiographic abnormalities and reactions to sugammadex that were anaphylactic or anaphylactoid in nature.

[Slide 6]

I will discuss both these issues in turn, beginning with the electrocardiographic abnormalities.

[Slide 7]

Three deaths were reported for subjects who participated in the clinical trials. Two occurred among sugammadex-treated subjects and one occurred in a placebo-

treated subject.

[Slide 8]

One of the deaths in the sugammadex-treated group involved a 65 year old woman who presented for resection of colon cancer. Her past medical history was significant only for hypertension, peptic ulcer disease and rheumatoid arthritis. She was randomized to receive 0.5 mg/kg of sugammadex which was administered following an uncomplicated surgery.

At 23 hours after her procedure the subject was noted to be in atrial fibrillation and respiratory failure. It was not indicated in the case report form whether this was the time of onset or the time of discovery for these events. The case report form indicated that the subject received no medication for the treatment of either condition, and stated that she recovered with sequelae, which were not specified. The subject died on postoperative day 42. The causes of death were listed as myocardial infarction, cardiogenic shock and pulmonary edema.

[Slide 9]

Based on the information submitted it is not possible to rule out that atrial fibrillation following

administration of sugammadex might be related to the use of the drug. As for the other two deaths, there was substantial evidence and a strong rationale to attribute their causes to something other than the study drug.

[Slide 10]

In this slide are the serious adverse events reported by preferred terms for system organ class. Cardiac, and QTc prolongation, which is part of the investigation systems organ class, are shown. The serious adverse events are, as before, broken down by study drug and dose.

In the top row the totals are reported along with percentages based on number of subjects exposed. It should be noted that not all preferred term SAEs are listed so the totals are in some cases greater than the sum of the counts that are actually shown. Blank boxes indicate no events had occurred. Some of the preferred terms, such as coronary artery disease, were not considered relevant to the administration of study drug and terms such as those were left out.

Of note in the table are the rhythm-associated events which occurred in the sugammadex-treated subjects,

that is, atrial fibrillation, cardiac arrest, electromechanical dissociation and ventricular tachycardia and the number of occurrences of QTc prolongation which were seen in sugammadex and placebo arms but not in the neostigmine-treated subjects.

In addition, the percentages of QTc prolongation that occurred in placebo-treated subjects was generally less than that observed in the sugammadex-subjects. It is important to note that there was no dose dependence for QTc prolongation in the sugammadex-treated subjects.

[Slide 11]

In this slide is a table similar in design to that on the previous slide. In this table cardiac-related adverse events that did not rise to the level of a serious adverse event are listed. Again, the number of occurrences in the sugammadex-treated arm generally exceeds those in the placebo arm and lower dose neostigmine arm as well. In some instances the occurrences in the sugammadex-treated arm also exceeded those of the higher dose neostigmine arm as well.

As in the previous slide, not all the preferred term SAEs are listed so the totals are in some cases greater than the sum of the count shown. But I should point out

that a total in percentage values for the 0.5 mg/kg sugammadex group is not accurate. The numbers should be eight total AEs and six percent. I apologize for the error.

Also similar to the previous table are the rhythm-associated events which occurred more frequently in the sugammadex-treated subjects.

[Slide 12]

The applicant has provided some information that may address the concerns raised by the data presented so far. Specifically, two thorough QT studies were conducted, one assessing the effects of sugammadex alone on QT duration and the other assessing the same effects but for sugammadex following the administration of a neuromuscular blocking agent.

The data from these studies appear to demonstrate that sugammadex, either alone or following the use of a neuromuscular blocking agent, does not significantly affect QTc.

[Slide 13]

The applicant has also evaluated differences in various components of the electrocardiogram by analyzing ECG recordings taken at similar time points for multiple

studies. The conclusions drawn from these data purport that sugammadex compared to placebo did not significantly alter either heart rate, PR interval, QRS duration or T- or U-wave morphology.

[Slide 14]

Now let=s turn our attention to the hypersensitivity reactions that occurred with administration of sugammadex.

[Slide 15]

In the adverse event database there were eight reports in total for the preferred terms hypersensitivity and drug hypersensitivity. These occurred in the dosing groups listed and do not suggest dose dependency.

[Slide 16]

If we examine these eight subjects in more detail it is noted that only three had events that were temporally related to the administration of sugammadex. The time of the hypersensitivity reaction is relative to the start of administration of sugammadex. Four subjects experienced their adverse events prior to administration of sugammadex but shortly following the administration of other medications to which the applicant assigned causality.

For one subject the timing of the adverse event relative to the administration of sugammadex is uncertain. However, the nature of the reactions, periorbital swelling and itching, are consistent with a topical reaction to an irritant such as the bepanthen to which the applicant attributed this subject=s hypersensitivity.

[Slide 17]

In this slide the signs and symptoms associated with a hypersensitivity reaction are listed for each of the three subjects whose adverse event was considered as likely related to sugammadex. While no treatments were reported to have been administered in response to these adverse events, the sugammadex infusion administered to subject 073, the third one down, was terminated due to adverse events experienced.

This subject also experienced prolonged QTc interval by the Bazett method, prolonged to greater than 60 milliseconds at one minute following termination of the infusion. Evaluation of the QTc for the Fridericia method was not similarly prolonged however.

It should be noted that no neuromuscular blocking agent was involved in these reactions, and that the dermal,

cardiac and gastrointestinal adverse events that were seen all consistent with those anaphylactic or anaphylactoid reactions.

[Slide 18]

This concern over risk associated with anaphylactic or anaphylactoid reactions led to a search of the adverse event database included in the safety database for this application. Four other cases of possible hypersensitivity reactions are not reported as such by the investigators. To this end, subjects with multiple adverse events that included dermal, cardiac and gastrointestinal reactions associated with anaphylactic or anaphylactoid responses were evaluated. This search identified 967 subjects who experienced a total of 1,628 adverse events.

[Slide 19]

This slide provides a breakdown of the number of subjects who experienced three or more adverse events specified by the search parameters. From these, six subjects were identified who had a skin reaction in addition to one or more cardiac or gastrointestinal adverse event.

[Slide 20]

This slide contains a list of subjects identified

in the search and the adverse event they experienced. The first subject, number 030, was the only one to have a hypersensitivity adverse event typically reported. All but one, which is number 003, had a cardiac and a GI adverse event in addition to the dermal reaction that was reported.

[Slide 21]

This slide shows the doses of sugammadex administered to these subjects, as well as the use or lack thereof of a neuromuscular blocking agent. There was no suggestion of dose or neuromuscular blocking agent dependence for these reactions. Of note for these subjects is that number 008 the sugammadex infusion was stopped prematurely due to the adverse events experienced. No other treatment for these adverse events was provided.

[Slide 22]

I would like to focus some attention on subject number 008 from the previous slide. According to the final study report, tryptase levels were assessed at one, three and six hours after significant administration. The one and three hour levels were positive in that they were greater than or equal to 15 Φg/L. The report also indicated that the subject had a positive result on skin prick testing and

intradermal testing months following the exposure. IgE was never assessed. These results led to the hypersensitivity study which was not conducted under IND.

Based on the findings for subject 008, at least one individual in 1,973, or 0.05 percent, was allergic to sugammadex. That was one individual with no previous exposure to the drug substance and for whom no predisposing risk factors could be identified. Study 19.4.110, the hypersensitivity study, not only confirmed the sugammadex allergy of subject 008, it also identified a second individual who had no reaction to sugammadex on initial exposure but had a positive intradermal test for the drug on follow-up evaluation.

While the argument was made by the applicant that this may be a false positive, the true status of that subject has yet to be determined. These findings, combined with the results of the adverse event database search which identified four additional subjects with possible allergic reactions, raised the concern as to whether this could be a substantial safety issue if the drug is used widely in clinical practice.

Either way, being able to identify patients

potentially at risk for an anaphylactic or anaphylactoid reaction would be important. The applicant has investigated the possibility of cross reactivity between sugammadex and beta lactams for subject 008 but failed to find a connection.

[Slide 23]

An alternative possibility is that cross-reactivity may exist among the cyclodextrins. The table in this slide lists the currently approved beta-cyclodextrins that are marketed in the United States.

The possibility that exposure to these products may sensitize individuals to sugammadex, and vice versa, may be worth exploring not only to fully assess the safety of sugammadex but to determine whether exposure to sugammadex may limit the use of other drugs, some of which have life-saving indications, such as the antifungals.

[Slide 24]

In summary, I note again that the evaluation of safety is ongoing but that the preliminary findings have not been inconsistent with those of the applicant. To date, two issues have been identified that may have a negative impact on the benefit/risk analysis.

First, are the electrocardiographic abnormalities that were discussed, including arrhythmias and QTc prolongation. The thorough QT studies still under review did not demonstrate that sugammadex posed a risk. The applicant=s analysis of the ECG components similarly indicated no sugammadex-related risk.

If the Division=s review fails to identify a substantial risk associated with sugammadex and the adverse event observations, and also confirms the applicant=s findings from the QT studies and ECG analysis, labeling and postmarketing adverse event monitoring are possible means for addressing the issue.

The second issue is the finding of at least one healthy subject, and possibly others, who experienced an anaphylactic or anaphylactoid reaction to sugammadex. The implications of the potential hypersensitivity reaction, with no ability to identify a priori patients who are at risk short of skin prick testing or intradermal testing, needs to be weighed with the potential widespread use of sugammadex if approved.

I thank you for your attention and look forward to your input and will be happy to answer any questions you may

have about my presentation.

DR. FARRAR: Next is Adam Wasserman.

Preclinical FDA Response

DR. WASSERMAN: Good morning.

[Slide 1]

I am Adam Wasserman. I am supervisory pharmacologist in the Division of Anesthesia, Analgesia and Rheumatology Products, and today I am going to talk a little bit about the nonclinical findings in bone and teeth with use of sugammadex in nonclinical models.

[Slide 2]

The first thing I want to say is that the review of the submitted studies is currently ongoing, as you have heard from prior presentations. I just felt that several issues would benefit from further detail or clarification. In particular, the safety margin descriptions that were based on bone concentrations as described by the applicant; the use of data for predicting the safety margin in pediatric patients, which I note is not the subject of this particular application but clearly is one that they are planning to pursue.

I will briefly mention some study endpoints and

parameters in the adult and juvenile animal studies and how that impacts safety margins that have been stated; some bone and teeth observations at doses at or above the no observed adverse effect level, NOAEL. This is a level at which there is some effect seen but it is considered not to be sufficient to sort of be called adverse. This is in contrast to NOEL, which is no observed effect level and that is a level at which there is no effect seen whatsoever.

I am not going to talk about it further, other than this point, there was no positive controls used in the bone evaluations to mimic anabolic or catabolic states to demonstrate assay sensitivity. Nevertheless, the parameters that were being used are considered to be sensitive, both the serum and urine, biochemical markers, as well as micro-CT. It would be helpful in some of our evaluations.

[Slide 3]

In regards to the safety margins described in the presentation, they were estimated using bone concentrations of sugammadex at the 4 mg/kg dose, at the routine reversal dose, and that generates a 4.5 Φg bone estimated as estimated by the applicant. However, they are requesting approval up to 16 mg/kg of sugammadex. This generates

estimated 18.5 Φg/g bone concentration. So, in this particular case one should consider reducing the safety margins approximately 4-fold for this highest dose.

In the bone studies in the young adult rat the no observed effect level with single dosing provides for a safety margin with the 4 mg/kg dose about 70-fold, as described by the applicant. When considering the 16 mg/kg dose, a single dose of sugammadex falls to about 17-fold.

The applicant introduced detailed bone-specific observations, including micro-CT which they described a little bit. But I wanted to mention what was seen above the NOEL. In a prior study there was a slight resorptive effect on trabecular bone parameters and a slight reduction in bone strength in one of several assessments.

In particular, this is femur indication stiffness that gets at the mechanical strength of trabecular bone. This was observed at study day 21 after a single dose, so three weeks after a single dose is where they picked up this slight reduction in bone strength on this parameter. This was not observed at six weeks post dose, indicating that there was some apparent recovery of this finding. There was no earlier evaluation of bone strength before that third

week to know if there was anything more significant.

In a four-week study with repeated dosing, intravenous dosing daily with sugammadex, the no observed effect level provided for a safety margin of 1,000-fold which, when considering the 16 mg/kg, would drop to about 270-fold.

Now, the much higher safety margins described here in this four-week study compared to a single dose study are primarily for two reasons. One is that with repeated dosing there is repeated accumulation in the bone that can be estimated. Also, there were fewer bone-specific observations that were made by the applicant in this study.

They did do an expanded histopathology with semiquantitative evaluation of bone mineral density but there was no micro-CT for trabecular or micro-architecture or any bone strength assessments. So, this number should be taken in context when considering the data from single dose. Nevertheless, there was nothing that was particularly striking found in that study at that dose.

[Slide 4]

When we go to the juvenile rat bone studies the no observed adverse effect level with four weeks of daily

dosing, intravenous dosing, provided for a safety margin about 1,000-fold according to the applicant at 4 mg/kg. Again, this would drop to around 270-fold with the 16 mg/kg dose.

They did observe effects on femur micro-architecture, with an increase in trabecular bone mineral density, thickness and number. It was noted at the end of four weeks of treatment. This was reversible by eight weeks of recovery after those four weeks. Femur size was not different at the end of the treatment but it was considerably smaller at the end of the recovery period, which was coincident with decreased body weight gain. The relationship of femur size to decreased body weight gain is certainly possible.

We note that the micro-architecture findings were not exactly temporally correlated as these preceded decreased body weight gain and, in fact, were not found at the end of the study when femur size was noticeably different.

I will also note that, in contrast to the young adult rat studies, bone strength testing was not conducted in the juvenile rat.

The bone concentration data that they developed is estimated in humans from mass-balance studies where they looked at retention of drug in adults, and where bone formation is going to be more limited and, therefore, sugammadex incorporation to bone would be much less. In the pediatric population the deposition of sugammadex in bone is likely to be higher.

Just to recap some of the data they showed, in the adult rat about three percent of a single dose winds up in the bones or is retained. In the juvenile rat about four times that, 13 percent of a single dose is retained in the bones.

[Slide 5]

In regards to evaluation of teeth in the juvenile rat study, the single dose no observed effect level was 48-fold or 12-fold depending upon the dose the 4 mg/kg or 16 mg/kg dose. However, I think we are in preliminarily in agreement that one observation of disrupted enamel in the incisors in a high dose animal represents probable background.

The more telling study is a 4-week juvenile study in which the no observed effect level provides about a 480-

fold safety margin based on the 4 mg/kg, and about 120-fold on the 16 mg/kg.

But just to note what was seen above this level, because it wasn=t addressed by the applicant, incisor discoloration was observed and malocclusion which occurs when the teeth grow inappropriately or overgrow a little bit the jaw and they can=t close the jaw well.

There was disrupted enamelization and deposition of amorphous material, which the applicant has not otherwise identified, in the incisors but it was noticeably less in the molars. All effects were much less in the molars.

We do agree that the rat molars may be more appropriate for risk assessment in adult and pediatric patients in which the enamelization process has been completed, and typically this is considered to be eight years and older. However, the incisors may be a more appropriate surrogate endpoint, if you will, for very young children. However, there is a significant safety margin here.

[Slide 6]

So, at this time our preliminary conclusions are that we are in agreement with the applicant=s assertion that

there are significant safety margins for single-dose use in adult patients on the observed effects on bone and teeth, based on the data that they have obtained from studies in young adult and juvenile rats. Additionally, the probability that a limited amount of sugammadex is going to go into the mature skeleton we find to be reassuring.

[Slide 7]

That being said, although the sponsor used some very conservative assumptions when estimating bone and teeth deposition in adults, including the maximum possible retention in adults as well as the absence of rocuronium being on board, the estimated safety margins for use in the pediatric population, which again I emphasize is not the subject of this application here but is intended to be pursued.

The pediatric safety margin may be a little more narrow due to reasons which have been described, especially the rapid bone growth which is likely to produce greater deposition in the pediatric patients as compared with adults. So, the safety margin may be reduced and it would be reduced to an unknown extent. At this time we do not have pediatric mass-balance data to inform deposition

estimates.

Additionally, all safety margins assume single exposure in pediatric as well as adult patients. But in particular, the nonclinical data indicates prolonged retention in bones so 170 days is what they identified as the mean retention. Therefore, because of this long duration, although it is unknown what the duration is in humans but it probably is likely to be quite prolonged as well. So, repeated exposures in this patient population may result in accumulation and reduction of safety margins.

[Slide 8]

Three final points. The juvenile animal studies did not demonstrate marked effects. They did not incorporate bone strength testing at the end of treatment when there were some mild findings that were observed in bone micro-architecture.

Although the effects on juvenile bone micro-architecture reversed when evaluated 57 days after maximal deposition at the end of the 8-week recovery period, the effects of retention of sugammadex over longer periods, such as the half-life of 178 days in bone or at the time of skeletal maturity, has not been evaluated.

Finally, the applicant=s argument that fracture healing should not be impacted by sugammadex we find to be plausible, but it is yet unsupported by data in nonclinical models of fracture. That concludes my presentation.

Questions from the Committee

DR. FARRAR: We actually have 15 minutes before we are scheduled to have lunch. I guess what I would like to do actually, given that some of these presentations are fresh in our minds, is ask the panel whether they would like to ask questions at this point or whether we can do so after lunch. We can also come back after lunch and ask additional questions. Are there questions that people would like to address at this point?

DR. POLLOCK: I have a question.

DR. FARRAR: Good.

DR. POLLOCK: Would you like to comment about those couple of outliers in both 301 and 303? What the reason that those people were so far outside the range of normal might be in terms of recovery?

DR. SHIBUYA: The sponsor did their own analysis of the outliers and they might wish to speak to it. What I did was I identified them and I looked at the information that

was available to us. It is difficult to make conclusions but what I can tell you is my overall sense. They tended to be patients who had been blocked with vecuronium over rocuronium. At least one of them showed evidence of recurarization but the T_4/T_1 ratio fell back down again. Like I said, these are very preliminary observations because I don=t really have a comparator. But it did seem like a lot of them were treated with corticosteroids, other drugs that could potentially interfere but, like I said, it is very preliminary. I didn=t look at a subset of the patients who responded to look at the concomitant meds.

DR. NICHOLS: This is a question for Dr. Shibuya. Were all the patients who were enrolled actually included in the analysis of the results?

DR. SHIBUYA: Because of the nature of it, that it was a single-dose trial, etc., there was very little dropout, if that is what you are asking.

DR. BOEN: We would also have some comments on the dropout analysis, the outlier analysis. I would like to ask Dr. Terri Monk to address this.

DR. MONK: When they asked me to come in and look at this data I was actually very interested in the outliers

so I asked to review the data of the individual patients. Can I have the slide up?

[Slide E-192]

This is the vecuronium patients. You are absolutely right, most of the outliers did occur in the vecuronium group of patients. There were two in the rocuronium group but let=s focus on the vecuronium patients. This was a shallow block. You can see that there were two outliers in the shallow block patients. These were outliers for the primary endpoint, return of a Train-of-Four ratio to 0.9.

If you look down you will see that there is one outlier about 20 minutes for the return of TOF of 0.9 and one about 65 minutes. If you look down in the corner, it is slightly smaller but I can read it to do. I looked back then at the return of the Train-of-Four to 0.7 and 0.8 because for years we thought that return of the Train-of-Four to 0.7 was a gold standard for the endpoint. It is only in the last decade that we have increased it to 0.9 because we know that there can still be some respiratory depression and maybe regurgitation if you are not fully recovered.

But if you look at 0.7, which used to be our gold standard, you can see the first patient that had a return of TOF to 0.9 at 20 minutesB-2.3 and 4.3 minutes. So, the first patient had a return to a Train-of-Four of 0.7 at 2.3 minutes and 0.8 at 4.3 minutes.

The second patient there had a return of Train-of-Four to 0.7 at 2.2 minutes after injection and 3.7 minutes for a return of Train-of-Four ratio of 0.8. So, what happened here? Why then did it take for the last 10 percent of recovery this extended period of time?

Well, I can tell you as a clinical investigator exactly what was going on. We were giving these doses at the end of the case at which time the patients were moving their arms and waking up. Because we were also reversing the general anesthesia we were giving them and extubating the patient, the movement interfered with the mechanical recording of the 0.8, and I think that these are probably mechanical type things, that we could not get back to 0.9 because of the artifact that was occurring with the movement. But I think it is very reassuring to look at the Train-of-Four recovery in these patients to 0.7 and 0.8. Now let=s go to the next slide.

[Slide E-193]

This is also with vecuronium. I agree once again, there were more outliers than with the rocuronium dose. We had this group of patients and I just looked at those that were 12 minutes and above for return of the TOF ratio to 0.9. You can see the asterisks here. The asterisks here meant that the data was imputed, which meant that the patients were moving around too much.

When they were trying to get the final reading they could not get the monitor stable enough. If you have worked with a Train-of-Four monitor using a stopwatch, the arm has to be flat. You can=t have movement. If the patient goes like that it really interferes with the measurement.

So, these data were imputed. I looked at the way they imputed the data. It was done very conservatively in this trial. If they imputed data for patients who had a rocuronium/sugammadex combination they gave it the worst-case scenario, the longest time possible. So, that was here. When you go back and you look at the Train-of-Four return to 0.7 and 0.8, they are much shorter ones again. Next slide.

[Slide E-194]

I looked at the five cases in which there were outliers in the profound block study to determine what happened when they returned to a Train-of-Four ratio of 0.7 and 0.8. You can see Train-of-Four ratio returning to 0.7 for all five of these patients was pretty quick, six minutes of less.

For a Train-of-Four ratio returning to 0.8 there were a few people where actually it was longer and that probably goes along with differences in the patients, some inter-patient variability. There were some patients that didn=t respond quite as quickly. But this patient still returned to a Train-of-Four of 0.7 in less than 3 minutes and this patient had a Train-of-Four of 0.7 in 6.3 minutes.

If you want to put this in a clinical scenario, many clinicians don=t even use neuromuscular junction monitors. They are looking at tidal volume; can they lift their head; can they give you a good hand grasp. You cannot assess return of function using clinical signs at any level above a Train-of-Four ratio of 0.5.

So, none of these patients experienced any respiratory problems and if you had just been using clinical

guidelines to determine if they had full return of neuromuscular function you probably would say, yes, they did because they have been able to pass all of our tests. So, I found this data quite reassuring.

Does anybody want to ask me any other questions since I am up here? I am sure there will be debate on this.

DR. NICHOLS: So, is this the sum of the information you have on patients who dropped out prior to analysis after enrollment.

DR. MONK: You mean the imputed data?

DR. NICHOLS: Yes.

DR. MONK: The imputed data that wasn=t included, the four asterisks. We could get that for you and bring it back to you after lunch and give you those numbers exactly too. But I just included the data on the ones where it wasn=t imputed just because I was very interested in whether they really for a long period of time had a very deep level of paralysis.

DR. NICHOLS: Just one other question, were clinical endpoints of adequate ventilation and oxygenation included in the studies?

DR. MONK: Yes, they were. The clinician was asked

at the end of every case to evaluate, using clinical endpoints, at least in my study and I think it was consistent throughout the studies, whether there were any signs of clinical recurarization and I think there was a zero incidence.

And, in your study too there was none. We found no clinical sign. And, even in the few patients, if you look at the data file, where they said recurarization reoccurred, the definition by the company was that the Train-of-Four ratio fell below 0.8, and not something that we could clinically assess.

When you go back and look where their Train-of-Four ratios were, they were all above 0.6 so they were all above the level that a clinician could even indicate or even evaluate and see any signs of neuromuscular weakness.

DR. FARRAR: Any other questions at this time? Yes?

DR. EISENACH: I was a little confused and I wonder if you could restate your conclusion regarding whether there is a cardiac signal or not. And, if there is a cardiac signal, whether there were preclinical data that we didn=t hear evaluating various channels that might be responsible.

DR. SIMONE: I should point out that the review is ongoing so part of this involves getting the case report forms and looking for mitigating factors or things that would raise our level of concern, for that matter.

Since the studies were designed primarily to assess efficacy, safety is kind of a byproduct and it is hard to make definitive statements but we can look for things that would just raise a flag, and it was just the differences in the numbers that were enough to suggest that maybe it is noise; maybe it is just above the noise level. So, it is something that is going to have to wait for further review before I can give you a more firm answer.

The only thing I can comment on at this point is that the sponsor, or the applicant=s additional studies, the thorough QT studies and their analysis is reassuring if that pans out.

But it looks like nothing that resulted in life-threatening situations, although some of these arrhythmias can lead to a life-threatening situation and at this point it is something that looks like it could be monitored just to determine whether or not it is truly a problem later on.

DR. EISENACH: Yes, because I would imagine that if

you calculated confidence limits around those two tables that you showed of cardiac events they must overlap between placebo and sugammadex but there could be an effect size which was considerable. So, I guess you don=t have a true conclusion about whether there is something there that requires further evaluation, other than postmarketing surveillance, at this point.

DR. SIMONE: That is true. The only other comparator that we have is the neostigmine which is also useful. Unfortunately, since neostigmine is not approved we don=t have a safety database for that drug within the FDA to go back and look and make comparisons with it.

DR. WASSERMAN: And from the preclinical side of things, there appeared to be some limited inhibition in HRB channel assays that did not reach an IC_{50}, although I think it was maximally around 20, 22 percent inhibition at a pretty high concentration.

In another in vitro model of action potential prolongation there were some increases as well. About 40 percent I think was maximal. In vivo there was transient, mild prolongation in the QT that I think was maximally 7 percent. It was transient though and it went away. The

levels at which I think these were seen were quite high relative to the clinical exposure.

DR. FARRAR: Sorry, for the record could you state your name, please?

DR. WASSERMAN: Sorry, this is Adam Wasserman.

DR. FARRAR: I think we are probably ready for lunch. I would just like to summarize a little bit as to what we have been hearing this morning. There has been a presentation of efficacy with regards to light and deep neuromuscular blockade, and the efficacy data appears to be adequate for both of those with regards to both the agency=s presentationB-I am sorry, yes?

DR. BOEN: Would there be a possibility to make a point with regard to the QTc study at this point in time?

DR. FARRAR: Sure. Yes, as long as it is going to be short.

DR. BOEN: In that case I would like to ask Dr. Van Den Dobbelsteen.

DR. VAN DEN DOBBELSTEEN: Slide on.

[Slide]

We did perform two QTc trials according to ICHE-14 in humans. As was mentioned before, they both were

randomized, placebo-controlled, crossover studies.

The first study was 19.4.105 with sugammadex alone, as was mentioned earlier. Sixty-two subjects were included in that study. The 109 study was sugammadex with and without rocuronium or vecuronium and a positive control, moxifloxacin, was included in that one as well. Thirty-nine ECGs were recorded during 24 hours at baseline, day minus 1 and after treatment. Next slide, please.

[Slide]

These are the results for the first study so that is the study where we treated subjects with sugammadex alone both at therapeutic doses, which were chosen as 4 mg/kg and supra therapeutic doses, 32 mg/kg, and the control you see there, moxifloxacin.

You can see clearly that the two doses, both the therapeutic dose as well as the supra therapeutic dose of sugammadex, remained well below the level of regulatory concern, whereas the positive control, moxifloxacin, is well above the level of regulatory concern. Next slide, please.

[Slide]

In the other study where we compared sugammadex alone 4 mg/kg at a therapeutic dose, sugammadex 32 mg/kg at

a supra therapeutic dose, with sugammadex 32 mg/kg plus rocuronium and sugammadex 32 mg/kg plus vecuronium with moxifloxacin you see the same pattern. The doses of sugammadex in combination with neuromuscular blocking agents stay well below the level of regulatory concern, whereas moxifloxacin as the positive control is well above that.

DR. FARRAR: I think we will need to break now and we can come back to this matter again later. What we will do now is to break for lunch and return at 1:00 o=clock. Also, if I could remind the members not to discuss the topics here at lunch.

[Whereupon, at 12:00 noon, the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. FARRAR: I will call the meeting back to order. The next business is the open public hearing. There was no formal registration for this portion of the meeting. No formally indicated that they wanted to speak, however, we are open to the public if there is anyone that wishes to speak specifically at this time. Seeing no interest, we are going to move on. What we are going to do is to have the FDA summary of issues presented first and then we will come back to a question and answer period before we move into the discussion to cover a few remaining issues. I think the summary of issues will help us all get going again in terms of thinking about various components. Dr. Purucker?

FDA Summary of Issues

DR. PURUCKER: Good afternoon, everyone.

[Slide 1]

My name is Dr. Mary Purucker. I am the clinical team leader for this application in the Division of Anesthesia, Analgesia and Rheumatology Products. I would like to take a few minutes to review the major points from the Division=s presentations earlier today in order to set

the stage for the questions for the committee.

[Slide 2]

To this end, I will restate the proposed indications for sugammadex, then turn to efficacy, focusing primarily on the data intended to support the immediate reversal claim. Finally, I will review the selected safety issues about which we request the committee=s input. We note in particular a recent submission that is still under review in our Division.

[Slide 3]

Let me remind you that the review is still ongoing and our findings presented today are preliminary. Overall, our findings to date are not inconsistent with those reported by the applicant.

[Slide 4]

This slide shows the two proposed claims for this product which I will read, probably for the fourth time today but just to remind you. First, sugammadex sodium injection is indicated for routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium. Second, sugammadex sodium injection is indicated for immediate reversal of neuromuscular blockade

at three minutes after administration or rocuronium.

[Slide 5]

With regard to efficacy, the Division is in general agreement that the efficacy of sugammadex sodium for the reversal of neuromuscular blockade, both shallow and profound, has been demonstrated for the adult population. However, we are not fully convinced that the data used to support the proposed second indication for sugammadex, the immediate reversal of neuromuscular blockadeB-we are not entirely convinced by these data. We note that sugammadex was not studied in the natural or emergency clinical setting which would be the most likely setting in which the product would be used for immediate reversal.

As noted by Dr. Shibuya this morning, this calls into serious question any extrapolation of an immediate reversal claim to a CICV or Acannot intubate/cannot ventilate@ clinical scenario. Study 303 was a controlled clinical trial used to support the immediate reversal claim. We will soon ask the committee to consider clinical study 303 and to comment on its role for a CICV indication, and it will be articulated in question 1.

[Slide 6]

This slide is to remind the panel and the audience about the salient points in the design and conduct of clinical trial 303. This was a randomized, controlled trial intended to assess immediate reversal of neuromuscular blockade by rocuronium. The reversal agent was administered based on time, not twitch, such as the reappearance of T_2 or response to a Train-of-Four stimulation.

The two treatment arms were rocuronium 1.2 mg/kg IV followed in 3 minutes by sugammadex injection 16 mg/kg; the second arm, succinylcholine 1 mg/kg IV. The primary endpoint was the time from administration of the neuromuscular blocking agent until T_1 had reached 10 percent of its baseline value.

[Slide 7]

Regarding safety, the applicant has completed an extensive program to evaluate the safety of sugammadex. The exposure database of 1,973 subjects for a new molecular entity is consistent with well-recognized guidelines such as ICH E1A which recommends at least 1,500 subjects.

[Slide 8]

This slide identifies three issues regarding the safety database for sugammadex that fall into the general

heading of special populations. First, the population studied was dominated by relatively healthy subjects and, as described earlier by Dr. Simone, approximately 88 percent were of ASA class 1 and 2. There was a single ASA class 4 subject. We note that this may not adequately represent the target population that would be seen in clinical practice.

Second, the exposure database is comprised primarily of subjects who received a single dose of sugammadex and whose follow up was generally limited to the immediate postoperative period. We note that if this product is approved repeat exposure would certainly occur in clinical practice.

Consider patients who have sustained complex orthopedic injuries where recurrent operative management might be expected.

Finally, while we recognize this NDA does not include a pediatric indication, we are concerned about off-label use of sugammadex in this population. In addition, there is likely to be a pediatric development program in the future. In fact, we learned today that one was submitted.

[Slide 9]

This brings us to the nonclinical concerns

described this morning by Dr. Wasserman. There are no data in this application on the effect of sugammadex on bone healing in adult or juvenile animal models. Further, sugammadex has an extremely long retention time in bones, based on animal models, where a half-life is in excess of 170 days has been observed. This is a particular concern in rapidly growing and remodeling bone in which the uptake of sugammadex would be considerably higher.

At the present time, we consider these nonclinical findings to be a potential safety concern with regard to the future development of sugammadex for children and for adolescents. This will need to be more fully evaluated before a decision can be made regarding the approvability of this application. We will ask the committee for their input on this issue, which will be articulated in question 2.

[Slide 10]

Finally, we have received from the applicant a clinical study report included with an extended safety update. This is presently under review in our Division.

The clinical study report was comprised of the results of re-study of selected subjects who had experienced hypersensitivity or allergic reactions to sugammadex during

the clinical development program. This was a non-U.S. study that was not included in the original NDA and was also a non-NDA study.

A normal volunteer in one of the early safety and tolerability studies had experienced anaphylaxis or an anaphylactoid reaction on initial exposure to sugammadex. The subsequent evaluation of this subject was described earlier by Dr. Simone.

In particular, this subject=s tryptase was noted to be elevated in the aftermath of the event, which is consistent with mast cell degranulation. The subject=s intradermal skin test to sugammadex was positive on two occasions. In the current study in the new submission this subject=s intradermal test was confirmed positive on a re-test.

There is a second subject described in the new submission who had been exposed to sugammadex during the product=s development program and who had not experienced a hypersensitivity reaction on initial exposure. This subject was unexpectedly found to have a positive intradermal test to sugammadex on re-test, which brings to mind the possibility of sensitization during initial exposure.

At the present time we believe the allergic reactions to study drug reported in the NDA submission, added to this new data that is now in-house, constitute a safety concern that will need to be fully evaluated, again before a final decision can be made regarding the risk/benefit profile of sugammadex.

[Slide 11]

This brings us to the questions for the panel and I would now like to turn the podium over to Dr. Farrar.

Questions from the Committee (Continued)

DR. FARRAR: Thank you very much. Before we get to the specific questions with regards to the product at hand, I would like to go back to a number of questions that we were discussing before lunch and ask the panel whether there are specific questions they would like additional answers to.

DR. ZELTERMAN: Can I go first? Dan Zelterman. This is mostly to Dr. Shibuya and the application. Dr. Shibuya brings us the point of the outliers, and it is unclear where the starting point actually is. There was a question that you had moved it to see where the starting point is. Finally, is the question of imputation of missing

values.

This is a little bit scary. It is perhaps for a future analysis. There are statistical methods that do not require imputation of missing values. There is censoring. You drew the Kaplan-Meier curves. There are methods that we use for survival analysis in which we don=t know how much longer it is going to be until the event occurs, and we use these when the patient drops out of the study where the data becomes unreliable. There are methods to handle censoring. That is one.

The second point is that there are non-parametric methods that, again, don=t require imputation and are not going to be overly sensitive to the extremely long recovery times. The net effect is there will be a loss of the extreme significance.

Remember, all the p values I saw in the morning were 0.0001. You are not going to lose that. There will be some small loss of that extreme significance but it will still make a very good case showing that there is a big difference for your product.

DR. SHIBUYA: I am not a statistician so I will answer the question in a simple fashion. I will tell you

how I plotted the curves that I showed you in my presentation and then I am sure that the applicant can better explain the imputation method, although we do agree that the applicant used a conservative imputation scheme.

Basically, what I did was I took the SAS transport files. Because some of them were somewhatB-I will say the column was somewhat unclearly identified, I asked them to identify where the key efficacy data were and the imputed data which was the protocol-specified analysis, and all I did was literally line them up and made, in Excel, my Kaplan-Meier. So, I didn=t do any imputation of my own. The imputed values were those that were used per their imputation scheme.

DR. BOEN: I would like to ask Dr. Rietbergen to come up.

DR. RIETBERGEN: Henk Reitebergen, statistician. When we designed the trial we decided to use an ANOVA, two-way ANOVA, and in case of missing data we chose a method that must be in favor of us so it would be a conservative method. Can I have the slide on, please?

[Slide]

As you can see here, this is the way we have

imputed the missing data. We have done it in a conservative way, meaning that the relatively slow recovery times were imputed for sugammadex-treated subjects and relatively fast time for neostigmine-treated subjects. Next slide, please.

[Slide]

If I may give an example, suppose you have a subject for whom TOF 0.5 is missing but TOF 0.8 is available, then in case it concerns a sugammadex patient I calculate for all sugammadex subjects with regard to TOF 0.8 and 0.9 the difference in time it takes to come from 0.8 to 0.9 for all those subjects, and then calculate the 95th percentile, so a rather long recovery time or, rather, a long time from 0.8 to 0.9. At that time I add to the 0.8 of the subject who has a missing time for 0.9. Next slide, please.

[Slide]

For the neostigmine group, the comparator group I did the same, with one exception, that I calculated the 5th percentile, so a rather fast recovery time within that group. Yes, that is the way we have analyzed the data. When we designed the study we decided to use an ANOVA.

DR. FARRAR: Dr. Zelterman, do you have any

comments?

DR. ZELTERMAN: Well, thank you for explaining the imputation. I was suggesting that there are methods that don=t require imputation at all that would be more consistent with the Kaplan-Meier that SAS is using, for instance, and it would not require the imputation at all. Imputation gives us, statisticians, a bad name.

DR. FARRAR: I think actually the more important question, and let me address this question to whoever is appropriate to answer it, is that in looking at the data that were clearly outliers with regards to the T_4/T_1 ratio of 0.9 the person who was discussing with us about those patients suggested that, in fact, for the achievement of that ratio that were at 0.7 or 0.8 there was actually data for those points and that it was much quicker than we might imply from the data that was here.

So, I am having trouble understanding how many patients were true outliers, and that there was actual data that they took a very long time versus the imputed points. If somebody could help me understand that, how many patients were there where there were actual measurements of the time they got to 0.9 that were in the 64-minute range or the 30-

minute range?

DR. BOEN: Dr. Terri Monk has made some preparations there.

DR. MONK: Let me start with imputed patients first. Go to slide A-3. If you remember, I think Dr. Nichols asked me about data for the patients that I had the asterisks on that were imputed. Now you understand how they imputed the data. If you can put up the slide?

[Slide]

These are the four patients in the profound block who had imputed data. You can see that for the top two patients the investigator had actually written down numbers where he felt recovery had returned. But the company looked at the baseline and did not think the baseline was stable and was not confident that they should rely on these numbers so they imputed the data for the worst-case scenario. The first patient who had recovery of a Train-of-Four of 0.9 was on the graph as 18 minutes.

The investigator actually had recorded the recovery at 6.5 minutes but because they said the baseline was not stable enough on the graph they imputed data. So, you can see that for that patient the investigator thought

the Train-of-Four returned to 70 percent at 3 minutes, 80 percent at 6.2 minutes and 90 percent at 6.5 minutes. So, in my opinion this is not an outlier but to be conservative the company did call it one.

There was a second patient where there was also a wandering baseline and they did not feel the trace was adequate to judge. The investigator had said that the Train-of-Four returned to 70 percent at 1.6 minutes, 80 percent at 1.6 minutes and Train-of-Four at 4.3 minutes, but because of the conservative method the company called it 18.3 minutes. I would classify these two as not being outliers.

When you look at these other two, the last two patients who had asterisks, the last Train-of-Four was imputed in only the last two patients. They had real values that they thought were reliable for the 70 percent return and 80 percent return for one patient 4.3 and then 5.5 minutes, and for the last patient 6.5 and 13.2 minutes.

So, basically, when you go back and you look at Train-of-Four recovery, either based on the estimate of the investigator or on the real data up until that point, they do not look like outliers in my opinion.

DR. FARRAR: You showed a slide with rocuronium I think that showed a number of outliers. If you could go back to that slide?

DR. MONK: That would be the one with bar graphs. Put the slide up. Thank you.

[Slide]

DR. FARRAR: My question specifically is how many of those are imputed and how many of those are real?

DR. MONK: Four are imputed, these four, the ones I just presented, with a hatch mark above it. Those are the four patients I just presented. I have data on the other ones. If you go to the next slide, I think on the next slide are the other five patients that were outliers. Go to E-194.

[Slide]

This is actual data. None of this data was imputed.

DR. FARRAR: Those are the other five?

DR. MONK: Yes. So, you have seen the four which clinically didn=t really look as if they were outliers. These two look like outliers. Possibly, when you look at it there are two really big outliers out of the entire group.

But I think if you want to put into reference, when you look at the outliers with what we are commonly using that has never been approved for the indication, it is significantly better than the standard care that we have now.

DR. FARRAR: Thank you.

DR. POLLOCK: I have another outlier question. Just for clarification, Dr. Monk, all the outliers were vecuronium patients. Is that correct?

DR. MONK: There were two patients with rocuronium that were also outside. They had similar profiles where they returned much more quickly to 0.7 or 0.8 reversal. I remember two in the data set. The majority were on vecuronium and it has been shown that it takes a little longer to reverse.

DR. POLLOCK: The only reason I want to verify that is for the third potential indication because if you are counting on this drug to reverse immediately and save somebody=s life and there really are outliers with that group I think we would like to know that.

DR. MONK: Right. Let me just comment on that. The reason that in the indication they have not done a study with vecuronium is because they assumed--since the only

approved indication for rapid sequence with a non-depolarizer is for rocuronium at the 1.2 mg/kg dose, they assumed that this would be a rapid sequence scenario where people would be surprised that they couldn=t intubate and they had gone with very large doses.

DR. POLLOCK: So, would you care to speculate why somebody might be an outlier, I mean a true outlier not just mechanical?

DR. MONK: Well, you know, I can speculate. It is like everything else going on with inter-patient variability. Usually you see it in people with increasing age; possibly reduced circulation; maybe some differences in their hepaticB-although this isn=t hepatically metabolized so, actually maybe Dr. Boen may have some other ideas because, you know, this is not metabolized, it is just eliminated--probably the typical things that cause pharmacodynamic variability.

DR. FARRAR: Dr. EISENACH?

DR. EISENACH: I had a question for Dr. Miller. For someone who has thought about this for a long time, I wonder how you think the company should present these data to the practitioner. So, when I think of how we determine

doses in anesthesia, for some things like general anesthetics we like median values.

We understand what a MAC is. You know, that is a concentration at which half of the patients move and half don=t. It is not particularly useful clinically but it is a number we are used to. With neuromuscular blockers, particularly for rapid sequence induction, we don=t think of ED_{50} values. We think of multiples of ED_{95} values because we want to be assured that we will get almost all the time a very profound effect very rapidly. Similarly, when I do spinal anesthesia I don=t choose an ED_{50} value, I choose a very high efficacy value.

So, if you are telling a clinician that this dose of drug will reverse paralysis to this ratio by a certain amount of time, I am just curious about your opinion. Should we be telling clinicians an average time or a median time, which is what you are doing, or should we be telling them when 95 percent of people would be reversed? It is particularly important I think for this immediate reversal question.

DR. MILLER: You asked an awful lot of questions in that one statement and I am not quite sure where to start.

With regards to endotracheal intubationB-I realize you are heading towards the antagonist, but just to go back a bit, the 1.2 mg/kg of vecuronium is given because it happens to mirror very well not only the mean but the variability associated with a comparable dose of succinylcholine. So, that is how we got at that particular dose

The companyB-I am obviously very biased-Bhas nicely shown I think efficacy for all three indications, although I understand that one of the indications is under question. Those certainly will serve as guidelines. I have no doubt that clinicians, when they use it, will try and figure out exactly what the doses should be in routine practice.

As you well know, I think it is common practice that either 2.5 or in some cases 5 mg per 70 mg of neostigmine is used. But those numbers came about after long years of clinical practice and I think that will happen here.

I have a feeling I am not answering your question as directly as--

DR. EISENACH: Well, I started in a very long and confused way. I guess what I was trying to say is that for

some things anesthesiologists are trained to understand average values, like MAC, and for other things we are trained to understand that we are only able to give this drug once since we want a very effective dose.

DR. MILLER: Right.

DR. EISENACH: Now, you haven=t done really dose response, the company hasn=t, and that is understandable. But my question is in terms of presenting how rapidly this reverses neuromuscular blockade, do you think the average is telling us what we want to know, or is the 95th percentile more important to the clinician, or do they need both?

DR. MILLER: I think it is the same answer I would give with our currently used drugs which have more variability than sugammadex does. That is, we tend to use drugs and be alert to the fact that once in a while we will end up with an outlier, and we enlarge the dose as a general principle when we want to make sure that we are maximizing the narrow variability. And, I think you are about to get more information.

DR. BOEN: I think that Dr. Monk also wants to add a couple of things with regard to this issue.

DR. EISENACH: If I can clarify also, I mean, if

the clinician is told that it is going to reverse a shallow blockade in 1.9 minutes would it be useful to have the 95th percentile be 10 minutes so that you would realize that actually clinical variability could be as long as 10 or 15 minutes?

DR. MONK: Yes, let me address that point. I think that we should, just as you are saying, tell the clinician the median, the mean and the 95th percentile. No doubt about it. I also think that the clinician is going to look at those numbers and forget them pretty quickly. He is going to say this works faster than neostigmine, and I think what in reality is going to happen is just what happens today, we go ahead, we reverse the block.

I use a neuromuscular junction monitor because I look for fade, and that, but I understand many clinicians do not and they are using the standard clinical criteria of head lift and hand grasp. And, I think when we are presenting this drug we need to tell them that numbers are numbers but clinical judgment is the most important thing and they need to keep administering this drug and looking for signs of reversal just as they would with neostigmine.

DR. BOEN: Another comment from Dr. Miller, please.

DR. MILLER: I just wanted to quickly comment. That is, we go through these details and discussions and I think it goes without saying that whether you are using neostigmine or sugammadex we think, and I think, sugammadex is very superior. It doesn=t negate the need for the clinician to watch and monitor the patient very carefully as they evolve out of general anesthesia, which includes paralysis, into the recovery room.

DR. EISENACH: I agree, it is a novel drug. It is an innovative drug. It is an interesting drug and it has many advantages, but if, as Terri Monk suggests, at some point the clinician may need to administer another dose I think having some information about how long they should wait until that is an appropriate thing would be useful.

DR. BOEN: I think Dr. Scott Groudine also would like to add some final words here.

DR. GROUDINE: Scott Groudine, I was one of the principal investigators on the Phase II dose-finding study from deep block. Could we put the slide up?

[Slide]

These are the summaries from my study and you can see that basically at the recommended manufacturer=s dose of

4 mg/kg-Bthis is not an emergency situation; this is just for routine reversalB-the longest that we had to wait was 4 minutes and 28 seconds from that study, with a mean of 2.3. So, it is really hard to tell the clinician, well, if you give them 4 mg--unless it is an emergency situationB-if you give them 4 mg you are going to reverse but some people reverse in 2.

And, you can basically see from the graph that starting at about 2 mg people are probably limited by their cardiac output to how fast they can reverse. There are always people who are very, very fast responders and as you get to bigger doses you totally eliminate outliers. I mean, everybody responds right away.

I think that also is a weakness of the TOFwatch. The TOFwatch, as Dr. Monk said, is very, very sensitive to movement, and everything. So, if you are going to take five minutes to recover and you are at end of a case people are going to start to move and wiggle, the surgeons are bumping against you, and it is very hard to get to that 0.9. Again, as was mentioned before, 0.9 is complete recovery; 0.9 means you can swallow; 0.9 means I can put a tongue depressor in your mouth, you can bite down on it and I can=t pull it out.

And, most clinicians don=t have the means or a TOFwatch to actually know when they are at 0.9 and there have been studies to say that a lot of patients end up in the recovery rooms at 0.6, 0.7 and 0.8 and are ventilating well but they could be better as far as aspirations, response to hypoxia and things like that. But clinicians are probably not going to uniformly use TOFwatches to know exactly when they get to 0.9.

So, as far as clinical markers go, patients will be fully recovered as far as the anesthesiologists can tell and you can see that actually giving larger doses-Bwe have gone up to 16 in the study that I was involved in-Bhas not been associated, with the patients that I have been involved with, with any serious adverse events, and you can always give a little bit more if time is of importance unless we are in the emergency situation.

And, I would like to address the 303 study a little later when somebody wants to talk about that because I was also a principal investigator on that.

So, you can see that the variability goes down and it depends on what you do. If you absolutely for some reason need the patient to be at 4 mg/kg almost everybody in

my study was reversed in 5 minutes, most were in 2. So, basically if we say the average is 2 I don=t know if the physician loses anything if he actually has to wait 4.5 minutes.

DR. FARRAR: Dr. Soriano?

DR. SORIANO: Well, the issue of dose is important because, as Dr. Eisenach mentioned, you are getting this really narrow range of time with higher doses and certainly that is what the clinician wants. Many of your studies, particularly in the elderly patients and renal failure patients or compromised renal function patients were done at 2 mg/kg.

Dr. Monk mentioned that in her own normal group of elderly patients some of them may have marginal renal function. So, if you start to push the dose to 4 mg/kg or 8 mg/kg perhaps you may start seeing a clinical marker of renal compromise or renal failure at that dosing regimen.

So, I know your last slide in your presentation mentioned the fact that patients with severe renal failure will be stated separately. Are you going to address this issue in this group of patients?

DR. BOEN: Yes, definitely. That is actually one

of the reasons why we would investigate that study group because we do see that group as a more vulnerable group and would like to study that group in a more prolonged situation, with a prolonged, if you wish, exposure of the compound to these patients.

DR. FARRAR: One of the issues that was brought up in the FDA discussion was that of the hypersensitivity group of patients. We heard that the hypersensitivity information that you provided for us today is new to the agency so they have not had a chance to look at this and to review it adequately. But I wonder if you have a sense from what was presented by the agency as to whether all of the patients that they identified through their analysis were, in fact, included in your hypersensitivity study.

DR. BOEN: I think we had a slightly different approach but I would like to ask Dr. Mirjam Mol, who is our safety representative, to present those views.

DR. MOL: Thank you. Mirjam Mol, safety. I would like to comment that, indeed, the one patient that presented with hypersensitivity, probable hypersensitivity, was in our Phase I study, the healthy volunteers and presented with mild to moderate symptoms that were self-limiting. But

based on that, indeed, we proceeded further with the skin testing and it tested probably hypersensitive.

After that we first designed the skin study that was recently submitted, and in that skin study we looked at all healthy volunteers from 156 healthy volunteers and evaluated them for any alleged hypersensitivity symptoms to make sure that from that group we will cover everybody and that we will put them in our skin study.

In addition, we also looked at our available database in patients that were anesthetized, as also FDA presented patients. I would like to have the following slide, please. Slide up.

[Slide]

First we looked at all symptoms that were there in the database that were remotely connected to hypersensitivity responses. These are responses we saw in healthy volunteers that were probably hypersensitive, and some other things that are symptoms that come up with hypersensitivity.

As you can see from this list, when you compare to placebo you see hardly any difference between the groups. So, based on the total groups we do not have any signal that

there is an increased risk. Of course, the total group is one. You should look at the individual patient as the FDA did and see whether there are any combinations of symptoms. But besides looking at combination of symptoms, it is also important to look at time relation and the surgery that is being performed. So, if I can have slide A-4?

[Slide]

FDA mentioned in their presentation four subjects from our Phase II/III program for patients that were anaesthetized that they consider to be potentially hypersensitive based on the symptoms. When you look at the symptoms that occurred those are, indeed, symptoms that can be related to hypersensitivity but when you look at the events themselves and when they occurred and the type of surgery that is being performed, you see thatB-I would like to go through those four patients that were presented earlier-Byou see that the first patient had a laparoscopic assisted colon resection and shortly after he had a recovery he presented with mild nausea and vomiting for the rest of the afternoon. Pruritus came in at the end of the day until the next day. Next slide, please.

[Slide]

The other subject received 4 mg/kg. He had a fissurectomy and hemorrhoid resection and sphincterotomy. This patient presented, indeed, with nausea and rash, and again nausea later. But when you look at the time relation you see that the nausea only occurred at day 2 and the rash at day 7 and also, again, the nausea at day 7. We consider the time relation not relevant to the hypersensitivity response. Next slide.

[Slide]

The third subject had an anterior vaginal repair. Abdominal pain was reported from day 1 to day 5. Pruritus started at day 2 and also the nausea started at day 2 and 3. Next slide, please.

[Slide]

The last patient that was presented by FDA had an abdominal hysterectomy and, again had pruritus from day one to four, nausea for a long time, vomiting for a long time, and she had procedural hypotension reported on day one, and it was specifically stated by the investigator that this was related to the anesthetic procedure.

So, based on these results I think, at least in our evaluation that we did for anaesthetized patients, we

are very confident that we did not identify any patients with mild hypersensitivity reaction. Furthermore, with respect to the healthy volunteer that did present with a probable hypersensitivity response, I would like to state that, as far as I am a clinician, it goes a little far to state that it was an anaphylactic reaction.

I think definitely it is hypersensitivity, with mild to moderate symptoms, that is self-limited but for anaphylactic reaction I have a completely different perception of what that is. It is much more pronounced and much more severe.

In addition to this, I would like to ask Dr. Monk whether she can give her opinion about the data that were represented.

DR. MONK: As a clinical investigator in the study, the company was extremely careful about collecting data on any AE that occurred and, as you can see, there was a large number of AEs in both groups and they didn=t differ between the groups.

So, in looking and reviewing these slides over the luncheon hour, the patients that were presented as possible hypersensitivity, they are patients who were having major,

usually intra-abdominal surgery, sometimes laparoscopy which is associated with postoperative nausea and vomiting. Pruritus can occur because these people are getting opioids for pain relief after surgery. I think anaphylactoid or anaphylactic is really a stretch, especially since, you know, even the one subject who was possible and was self-limited and didn=t require any medication or treatment is really a stretch and, at best, the data really shows one person who has hypersensitivity and not really any evidence of anaphylactoid reaction.

DR. PURUCKER: I would like to ask how you interpret the tryptase then.

DR. MOL: The increase in tryptase we saw in these healthy volunteers was 19.9, if I remember correctly, and this is when you compare it to a full anaphylactic reaction where you have a massive degradation of mast cells then this is considered to be marginally increased.

DR. PURUCKER: But it still indicates mast cell degradation, which means there was potentially IgE on the surface, cross-linking, and it was either anaphylactic or anaphylactoid reaction.

DR. MOL: Indeed, you are right, it can be IgE

mediated. In addition to that, we are also working on a test for antibodies which we can detect for sugammadex but, indeed, you need a test to really show there are also other mechanisms that could support the mast cell release. But, indeed, IgE is a possibility.

DR. PURUCKER: Yes, IgE would be anaphylaxis. Just by virtue of there being tryptase there was mast cell degradation. That is the only point that we are trying to make and anaphylaxis is not necessary a measurement of degree or clinical presentation. One can have very mild forms of anaphylaxis.

DR. BOEN: Well, tryptase releases definitely a mediator for anaphylaxis but it can be, even especially at lower ranges, an indicator of mast cell degranulation due to compounds that have a direct effect on mast cells. For instance, the benzylisoquinolines are known to have such an effect on mast cells.

DR. PURUCKER: We are in agreement, that would be an anaphylactic reaction. Thank you.

DR. FARRAR: Let me ask the panel, since this is an area where, as Dr. Simone said, you are in the beginning of the process or the process is ongoing, clearly additional

information can be looked at and the various patients that you found versus the ones that the company is reporting need to be resolved, but given the fact that every drug has the potential for a person having an immune response, anaphylaxis or a lesser response, it would be surprising if this drug didn=t have at least one or two patients that showed up with some response that was unexpected.

The question to the panel before we get to the formal questions is just whether there are any thoughts that you have or whether there is any additional information that you would be interested in having with regards to that potential response that would help in clinical practice or in use of the drug.

DR. ARONSON: I am not sure how this may or may not relate but I am wondering about immunosuppressive drugs. For instance, the RA patient that died, do you know the medications that the patient may have been on?

DR. BOEN: Dr. Mol, would you be able to answer that question? We are working on it; papers are flying.

DR. FARRAR: Well, perhaps we can give you a minute to find that and we can go to another question while we are waiting.

DR. BOEN: Yes, we need a minute or so.

DR. POLLOCK: While the papers are shuffling I will ask another question. I think you are exactly right, I think it would be unusual to expect that there wouldn=t be some patients in a group of 2,000 that wouldn=t have some sort of reaction to the drug, and I think what I would be interested in is some way that we could potentially identify those patients before they get their drug. I think that is really the thing we would like to know. Is there anything about that particular patient or any of the other patients that could be identified?

DR. BOEN: Well, from experience also in anesthesiology for instance in Europe with neuromuscular blocking agents where allergy is being reported, it is also known that prospective tests are not really helpful because of, you know, the limited sensitivity, the positive predictive value is actually quite low. So, you would have to test thousands and thousands of patients and still would end up, you know, with many, many false positives. So, there is an obvious problem there.

DR. POLLOCK: Well, I was not suggesting that patients be tested prospectively for sensitivity. I was

just hoping that by looking at the several patients that have been identified it would be ideal if something came up that was common in those patients= background, and I don=t think that is the case, is it?

DR. BOEN: Right. Dr. Monk has found the information.

DR. MONK: You wanted to address the medical history of the patient who died that possibly could have been related to the administration. Is that correct?

MS. ARONSON: The medications.

DR. MONK: Well, let me tell you a little bit about the patient. I was interested in her too after hearing the scenario so I looked at her at lunch.

She was a 65-year old lady who actually had a history of hypertension, peptic ulcer disease and rheumatoid arthritis, and she was on medications prior to surgery and I think you are correct that she was an immunosuppressant and she was also on a calcium channel blocker, and the immunosuppressant was for her rheumatoid arthritis.

Now, of interest is that this lady did develop atrial fibrillation and she was undergoing a bowel resection. The literature reports there is about a 20 to 25

percent incidence of cardiac abnormalities following this type of surgery in the elderly population, the most common of which is atrial fibrillation.

There was one prospective longitudinal study that looked at associated factors and they found the two most highly associated factors with this problem in the postoperative period was advancing age and history of hypertension. So, she had both of those things going on which would have predisposed her to this problem.

The other thing that she had was rheumatoid arthritis, and there have been autopsy studies that have shown that as many as 50 percent of people with rheumatoid arthritis have pericardial problems on autopsy. So, there is a high incidence of pericardial effusion in these patients which would also predispose them to developing atrial fibrillation or a rhythm problem in the postoperative period, especially if they develop any level of sepsis. Does that answer your question?

MS. ARONSON: Yes, thank you.

DR. SIMONE: I have one comment and one question. The patient that was considered to be hypersensitive to sugammadex initially was exposed only to sugammadex and not

to a neuromuscular blocking agent. While the patient received no medical intervention for the reactions that were seen, the infusion was stopped prematurely due to the reactions that were seen.

One of the problems we have with identifying adverse events that are related to drugs is the milieu of medications that many of these patients find themselves in, especially in the anesthesia setting. It is very difficult to tease out what is caused by one agent versus another or a combination thereof.

It is easy sometimes to find reasons why someone may have a reaction to a drug by explaining it away, and it is very difficult to prove causality. So, generally speaking, what we try to do is at least identify those adverse events that seem to occur following exposure to a drug and just use that in our benefit/risk analysis to the best of our ability to decide to what extent it has a negative impact.

So, while it may be difficult to even go through these, it could be quite possible to go through all the cases and identify possibly other causes or excuses. It is almost impossible to know for sure how much effect

sugammadex has actually had in terms of these adverse events, which is the nature of the beast.

DR. FARRAR: Do you have a response to that?

DR. BOEN: No.

DR. FARRAR: Go ahead, Dr. Nichols.

DR. NICHOLS: I was wondering if the applicant could go back to the slide on adverse events. You had a slide in which adverse events with sugammadex were compared to placebo and the FDA has two slides comparing the treatment drug with neostigmine. So, I was wondering if you could do apples to apples and compare the drug against neostigmine, and also include among the adverse events that you are looking at not just tachycardia but all dysrhythmias.

DR. FARRAR: So, the slide you just showed about ten minutes ago with the comparison of the events in both placebo and the treated group I think is what we are asking for. It is not in the book.

DR. MOL: If I can have slide S-185?

[Slide]

I can partly answer your question because what we did is that we looked at the adverse events compared to

neostigmine and we looked at those that were twice the incidence of neostigmine, either via sugammadex or the other way around. And, these are the ones that we identified. The left column is those adverse events that were identified at twice the incidence of neostigmine, which was flatulence and GI disorders perioperative, which was not further specified. These are preferred terms coded.

The other list is the adverse events on neostigmine at twice the incidence of sugammadex. Here, indeed, is dry mouth, anxiety. So these are really the differences. So, I hope this partly answers your question.

DR. NICHOLS: That is helpful but I think, just following on an earlier question from Dr. Eisenach, there is some uncertainty about the cardiac effects here and I was hoping that you could get us a bit more clarity on the cardiac effects in particular in comparison to the neostigmine.

DR. MOL: I don=t have a slide on that.

DR. BOEN: I am afraid we don=t have a slide at this time for you to see. Sorry about that.

DR. NICHOLS: Maybe Dr. Simone can project his slides from his talk as a reference.

[Slide]

DR. FARRAR: Dr. Nichols, is this it?

DR. NICHOLS: Well, this slide and one other one gives you the flavor that the incidence or the number of cardiac events seems to be bigger with sugammadex than with neostigmine. Perhaps I am misinterpreting that and, if I am misinterpreting that, then the applicant should correct me on this. But particularly with the 2 mg/kg dose there seemed to be a lot of numbers in there.

DR. FARRAR: Dr. Simone?

DR. SIMONE: It should be remembered that these studies were designed to assess efficacy. They were not designed to show a significant difference one way or the other in terms of the safety features. So, what we are looking for at this point is simply any kind of a signal, something to suggest that an event is occurring more frequently on one drug than the other.

It is not a rigorous statistical approach to dealing with it, it is just trying to identify possible differences. The data is what it is and the interpretation is open to the individual looking at it. But what we do see is that at least for some of the doses of sugammadex there

is a percentage of subjects who have a larger incidence than neostigmine or the placebo for some of these arrhythmias. Whether that is a true finding or just an observation is hard to say.

The other thing that is somewhat important anyway is that if you look across the doses of sugammadex it is not a particularly dose-dependent finding, which is somewhat reassuring.

DR. BOEN: Yes, I think one of the things is it is crowded with sugammadex of course but, on the other hand, it is not corrected for the numbers of patients that are in the dose groups with sugammadex. And, you are completely right, if you look at the dose proportionality there doesn=t seem to be one.

DR. SIMONE: Just to be clear, the percentages at the bottom are based on the individuals exposed at those doses, but the numbers for the individual preferred terms are just incidence. They are not percentages.

DR. EISENACH: I think my point about this when I asked you if there was a signal there or not is that you have overlapping confidence intervals so there is no difference between neostigmine or placebo or sugammadex in

these but you have an effect that may be real or may not be real.

Your response I think was that it was something that you would want to keep an eye on as we gain more exposure with the drug. That was my understanding of what you had said, not that there was a signal there we had to worry about necessarily.

DR. SIMONE: It was a suggestion as a possible approach to follow this drug when it went on the market for these types of adverse events and to include them in the labeling. But that is not to downplay their importance or to overemphasize their relationship to sugammadex.

DR. FARRAR: And just to be specific about this slide, the number that sort of jumps out at you because it is two digits and it is larger than the others is the 10 percent and the 6 mg/kg group. There are only 28 patients in that group to start with so the confidence interval is going to be very wide.

So, if we look at the average of the numbers across the proposed drug versus the neostigmine, the numbers are all sort of in the same range. I think that is what I am hearing you say. Is that correct?

DR. SIMONE: Yes.

DR. GROUDINE: Scott Groudine, one of the principal investigators in two different trials. From doing research, I will tell you that when you give neostigmine and Robinul to someone you would expect the heart rate to go up and people will not capture that as an adverse event.

That is why when I give sugammadex and the heart rate changes I am looking for that. When I give Robinul and neostigmine to a patient the heart rate goes up and then it goes down, and that often is not captured. When you look at the heart rate though, if we can see Dr. Miller=s slide--

[Slide]

B-although you see no tachycardias there, when you actually look at heart rate you do see a change in heart rate when you are looking at that. It is just that most investigators and research nurses will not consider if the heart rate goes up a bit after giving Robinul and neostigmine an adverse event. They might consider it much more strongly when they have given sugammadex.

DR. EISENACH: Are you implying these studies were unblinded studies?

DR. GROUDINE: No. Some of them were unblinded and

some were comparing, you know, neostigmine to Robinul and some were just pure sugammadex. You knew exactly what you were giving and there was no placebo or control.

DR. FARRAR: Go ahead.

DR. SIMONE: I cannot speak to the specifics of the clinical trials, perhaps one of the members of the applicant=s team can. But generally we request that in the pivotal trials the cutoffs that are used to determine whether a particular occurrence is an adverse event or not should be prespecified.

So, this is often done in terms of, like, a 25 percent deviation from baseline for blood pressure measurements or sometimes absolute values. But that is given so that there is a uniform assessment across the board.

DR. FARRAR: Any other questions before we go to the questions that are being posed to the board by the FDA?

DR. EISENACH: I don=t want to prolong this too much, but like neuromuscular blockersB-and Dr. Miller has studied this intensely in the pastB-there is very small penetration into the CNS. I understand in rats it is less than three percent.

I was just curious if you could look at and present to the FDA sometime from your data set any patients who you would expect to have the blood-brain barrier broken down, if you could look at adverse events in those patients in your data set of 2,000. I think it would be useful for the FDA to hear whether there was any signal in a group where you might expect a drug that normally doesn=t enter the brain to enter the brain.

DR. BOEN: I think that would be a very good discussion but we don=t have that data right here, as you can imagine.

DR. FARRAR: Any other issues anybody would like to bring up?

DR. BOEN: Our preclinical toxicologist would like to add some comments on that, if he may.

DR. VAN DEN DOBBELSTEEN: To be sure you understand me right, I am going to be presenting a slide with nonclinical data on it to give you an impression of what an imperfect blood-brain barrier would mean for this compound. We dosed pregnant animals with radiolabel and looked where the radiolabel would go. As I told you in my presentation, this would predominantly be in bone. Slide on, please.

[Slide]

In this slide you see rat embryo basically, and one would recognize that at early stages of embryonic development where the blood-brain barrier would not be quite intact but still there. You won=t see the compound getting through the blood-brain barrier. All the black dots you see are the bones that are being radiolabeled but there is basically no radiolabel in the brain even in the case of an imperfect blood-brain barrier. Slide off, please.

DR. EISENACH: Well, I think some human data would be very interesting. A fetal rat is interesting but different.

DR. FARRAR: Dr. Deshpande?

DR. DESHPANDE: I am still wondering about the developing bone, or bone development rather and the difference between juvenile and adult rats we have discussed before. The question that I have, I am thinking about the 170-day retention in bone in a developing child where many of our patients will be coming back for repeated procedures, and the studies that I have seen have not really addressed repeated exposure, particularly in the younger age group. So, I wonder if you could comment on the potential impact.

The reason I sort of harp on this a little bit is that even though the application is an adult application, the warning for succinylcholine is a pediatric warning for succinylcholine. So, what we are really discussing today is a drug that will be used in pediatrics even though the specific approval process is not really requesting a pediatric approval.

DR. BOEN: Could I have slide N-115, please?

[Slide]

DR. VAN DEN DOBBELSTEEN: To basically give you a better representation of how we have expressed our half-lives in this study is really in a worst-case situation. In my presentation I tried to refer to the half-life as a terminal half-life, which is really the worst-case situation that you will see.

Here, on the vertical axis you see the amount of sugammadex attached to the various kinds of bones and what you will see is that you have an initial phase, the wearing off of the compound, lasting approximately three weeks where you lose half the compound.

So, the long half-life is really based on the last three data points in this curve which represent basically