DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND LIFE SUPPORT DRUGS

ADVISORY COMMITTEE MEETING

Tuesday, March 11, 2008

8:30 a.m.

Hilton Washington, D.C./Silver Spring
Maryland Ballroom
8727 Colesville Road
Silver Spring, MD

PAPER MILL REPORTING
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C O N T E N T S

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Arthur Simone, M.D., Ph.D.
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P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. FARRAR: So, we would like to call this meeting to order, and the first order of business will be some introductions. Do you want to start?

DR. ROSEBRAUGH: I am Curt Rosebraugh, Acting Director, Office of Drug Evaluation II.

DR. RAPPAPORT: Bob Rappaport, Director of the Division of Anesthesia, Analgesia and Rheumatology Products.

DR. SHIBUYA: Bob Shibuya, Medical Officer for the Division of Anesthesia, Analgesia and Rheumatology Products.

DR. SIMONE: Arthur Simone, Medical Officer, Division of Anesthesia, Analgesia and Rheumatology Products.

DR. SORIANO: Sul Soriano, pediatric anesthesiologist at Children=s Hospital and Harvard Medical School.

MS. ARONSON: Diane Aronson, consumer representative.

DR. EISENACH: Jim Eisenach, anesthesiologist, Wake Forest University.

DR. FARRAR: John Farrar, neurologist and epidemiologist at the University of Pennsylvania.

DR. PHAN: Mimi Phan, Designated Federal Official, FDA.

DR. POLLOCK: Julia Pollock, anesthesiologist at Virginia Mason in Seattle, Washington.

DR. ZELTERMAN: Dan Zelterman, professor of biostatistics at Yale.

DR. NUSSMEIER: Nancy Nussmeier. I am an anesthesiologist at SUNY Upstate in Syracuse, New York.

DR. DESHPANDE: Jay Deshpande. I am a pediatric anesthesiologist/intensivist at Vanderbilt, in Nashville.

DR. NICHOLS: David Nichols, pediatric anesthesiologist, Johns Hopkins University.

DR. PROUGH: Don Prough, anesthesiologist, University of Texas Medical Branch at Galveston.

DR. McLESKEY: Charlie McLeskey, anesthesiology trained, currently working for Baxter and I am the industry rep for the committee.

DR. FARRAR: Just as a matter of note, Dr. Zuppa is not able to join us today. So, I will ask Mimi Phan to do the conflict of interest statement, please.

Conflict of Interest Statement

DR. PHAN: the Food and Drug Administration is

convening today's meeting of the Anesthetic Life Support Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and consultants are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committees compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC '208 and '712 of the Federal Food, Drug and Cosmetic Act is being provided to participants at today's meeting and to the public.

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

government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

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

Today's agenda involves discussions of new drug application NDA 22-225, sugammadex sodium injection, proposed trade name Bridion, sponsored by Organon USA, a subsidiary of Schering-Plough Corporation, proposed indication of routine reversal of shallow and profound neuromuscular blockade induced by rocuronium or vecuronium and immediate reversal of neuromuscular blockade at three minutes after administration of rocuronium.

Based on the agenda of today's meeting and all financial interests reported by the committee members and

consultants, conflict of interest waivers have been issued in accordance with 18 USC 208(b)(3) and 712 of the FD&C Act to Dr. James Eisenach. Dr. Eisenach's waivers cover unrelated consulting with the sponsor for which he receives less than $10,001 per year.

The waivers allow Dr. Eisenach to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/ohrms/dockets/defulat.htm. Copies of the waivers may also be obtained by submitting a written request to the agency=s Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Charles McLeskey is serving as the acting industry representative, acting on behalf of all regulated industry. Dr. McLeskey is an employee of Baxter Healthcare.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants

need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationship that they may have with any firms at issue. Thank you.

DR. FARRAR: Dr. Rappaport?

Introduction to Meeting

DR. RAPPAPORT: Good morning. Before I give my opening comments I would like to ask one of the committee members to come up here. Dr. Soriano, would you join me at the podium? Dr. Soriano has been a member of the committee for three years now and he is rotating off, unfortunately. He has been a valued member and somebody who we have turned to a number of times for help and assistance in difficult issues related to anesthetic drug products. We are very grateful for his service and I am sure we will be asking him to come back and help us out in the future. Thank you very much, Dr. Soriano.

DR. SORIANO: Thank you, Bob.

DR. RAPPAPORT: This is a little plaque to commemorate--

[Applause]

DR. RAPPAPORT: Good morning. Dr. Farrar, members of the committee and invited guests, thank you for participating in this meeting of the Anesthetics and Life Support Drugs Advisory Committee.

Today we will be discussing Organon=s new drug application for sugammadex, a novel agent for the reversal of neuromuscular blockade induced by rocuronium and vecuronium. Sugammadex is a modified gamma-cyclodextrin designed to form a 1:1 inclusion complex with a neuromuscular blocking molecule. Sequestration of the free neuromuscular blocker results in reversal of neuromuscular blockade.

Organon is seeking two indications, the routine reversal of shallow or profound neuromuscular blockade induced by rocuronium and vecuronium and immediate reversal of neuromuscular blockade at three minutes after administration of rocuronium.

This morning representatives from Organon will present an overview of their application. This will be followed by presentations from FDA and specific concerns that have arisen during the review of the application. These concerns are related to both the efficacy and the

safety findings, and also include preclinical data that could impact not only on our evaluation of the current application but on future supplements for the approval of sugammadex for use in the pediatric population.

As you will hear, the agency generally agrees that Organon has demonstrated the efficacy of sugammadex for reversal of neuromuscular blockade, both shallow and profound. However, the sponsor's second indication for the immediate reversal of neuromuscular blockade was studied in a setting which may not have adequately assessed the use of the product in the actual emergency settings in which it is likely to be employed.

In addition, Organon, within the last two weeks, submitted new data to the application from a study assessing hypersensitivity reactions in subjects exposed to sugammadex which raised safety concerns that will need to be fully evaluated before a final decision can be made regarding the risk/benefit profile of the drug. Indeed, this is such late-breaking news for us and, not giving ourselves a chance to review the information and have some discussion internally, we didn't really provide a formal question to the committee members to address this issue but we are going

to do so. We are going to be working over lunch.

Finally, the preclinical data raised concerns related to the deposition and extended inclusion of the drug in both bone and teeth.

This afternoon we will be asking you to discuss whether the applicant has provided adequate data to support the use of sugammadex in the setting of emergent need to reverse neuromuscular blockade. In addition, we will ask you to address how the preclinical data regarding the deposition of drug in bone and teeth, and the safety concerns related to allergic reactions, might affect the overall risk/benefit profile of the product.

The division and the agency are grateful to the members of the committee and to our invited guests for taking time from your busy schedules to participate in this meeting. Your clinical experience and expertise will be of significant assistance to us as we finalize our review of this potentially valuable new anesthetic agent. Thank you in advance for helping us to make the most informed and appropriate decision possible.

DR. FARRAR: Thank you, Dr. Rappaport. Could I ask the last member of the FDA panel to identify herself,

please?

DR. PURUCKER: Hi. I am Dr. Mary Purucker, medical team leader.

DR. FARRAR: Thank you. My job this morning is to try and drive this ship. What that means primarily is that I have to, along with Mimi Phan, direct the discussion today. We have a schedule and we will need to stick to that schedule, at least as best as we can, so just fair warning that if there are substantial overruns in terms of time we may have to cut off the discussion.

I also want to echo what Mimi has said, which is that we need to keep it in an orderly fashion. So, during the discussion and during question periods if you can just make sure that you make yourself known if I don't spot you, especially on the committee, please just speak up.

At this time I would like to call on June Bray, from Organon, to come and give the introduction, and then if you could introduce your team as they come up, that would be great. Thank you.

Industry Presentation

Introduction

MS. BRAY: Good morning. Mr. Chairman, members of

the advisory committee, FDA staff, ladies and gentlemen, we are very pleased to have the opportunity this morning to present to you an overview of NDA 22-225 for sugammadex.

[Slide 1]

Sugammadex is a novel new drug product that will enable anesthesiologists and physicians who use neuromuscular blocking drugs to rapidly reverse neuromuscular blockade induced by rocuronium or vecuronium.

[Slide 2]

Sugammadex is a first in class selective relaxant binding agent that encapsulates rocuronium or vecuronium, preventing either drug from binding to the nicotinic receptors and neuromuscular junction, thereby preventing neuromuscular blockade.

Sugammadex is an innovative drug product. It not only can reverse a shallow blockade, it is the first drug product that can also reverse a profound or deep block.

[Slide 3]

Throughout the development of sugammadex we have had numerous interactions with the FDA. While this slide only highlights our key interactions, we did wish to point out that prior to initiating our pivotal trials, 301 and

302, we did reach agreement with the FDA on the protocol design utilizing the special protocol assessment procedure. We also reached agreement with the FDA on the design of our dedicated QTc trial.

[Slide 4]

This NDA has been classified as a priority review, indicating that sugammadex has the potential to meet an unmet medical need.

[Slide 5]

Sugammadex is truly unique. It is the first drug product that can reverse a profound neuromuscular block. It can also provide immediate reversal in those clinical situations where it may be warranted, such as Acannot intubate/cannot-ventilate. Lastly, it avoids the need to use acetylcholinesterase inhibitors and muscarinic antagonists.

[Slide 6]

We are seeking approval for the use of sugammadex in adult patients, specifically for routine reversal of shallow and profound neuromuscular blockade induced by rocuronium or vecuronium, and for immediate reversal of neuromuscular blockade at three minutes after the

administration of rocuronium.

The data submitted in this application support the safety and efficacy for use of sugammadex in the adult patient population. We do plan to seek approval for a pediatric indication and have recently submitted our pediatric development plan to the FDA for review.

[Slide 7]

The dosing recommendations for sugammadex depend on the level of neuromuscular blockade to be reversed. I would like to add that as part of our clinical trial design we used a Train-of-Four stimulus or twitch of four monitor to be able to objectively measure the level of neuromuscular blockade. For our dosing recommendations for routine reversal of a shallow blockade, which is defined as spontaneous recovery that has occurred up to the reappearance of T_2, a dose of 2 mg/kg is recommended following rocuronium- or vecuronium-induced blockade. For reversal of a profound blockade, defined as recovery that has reached 1-2 post-tetanic counts, a dose of 4 mg/kg is recommended following rocuronium- or vecuronium-induced blockade.

[Slide 8]

In those situations where immediate reversal may be required, a dose of 16 mg/kg is recommended three minutes following the administration of rocuronium. We wish to point out, however, that we have no data to support the use of sugammadex for immediate reversal following vecuronium-induced blockade.

[Slide 9]

Following my introduction, Dr. Ron Miller, Professor and Chairman, Department of Anesthesia and Perioperative Care, University of California San Francisco School of Medicine, will address the unmet medical need in reversing neuromuscular blockade.

Next, Dr. Anton Bom will present the mechanism of action and pharmacology and pharmacokinetics of sugammadex. This will be followed by a presentation made by Dr. Diels van Den Dobbelsteen who will present a nonclinical safety overview. Dr. van Den Dobbelsteen will also be addressing question number two that has been posed to the committee.

Next, Dr. Patrick Boen will present a clinical overview of our efficacy and safety data. Dr. Boen will also be addressing question number one regarding the clinical relevance of our immediate reversal trial, trial

303. Lastly, Dr. Miller will be making our closing remarks.

[Slide 10]

In addition to Dr. Miller, we are very pleased to have with us the following consultants: Dr. Terri Monk, Professor, Department of Anesthesiology, Duke University Medical Center; Dr. Scott Groudine, Professor of Anesthesiology, Albany Medical Center.

In addition to our expert anesthesiologists, we are also very pleased to have with us today Dr. Harry Genant, Professor Emeritus, Departments of Radiology, Medicine and Orthopedic Surgery, University of California San Francisco. Dr. Genant is a leading expert in evaluating non-clinical and clinical bone data.

[Slide 11]

It is now my pleasure to introduce Dr. Ron Miller.

Unmet Medical Need

DR. MILLER: Good morning and thank you very much. I am delighted to have the opportunity to describe the unmet medical need with regard to reversal of neuromuscular blockade. For many years I have been involved with research in clinical neuromuscular pharmacology and specifically with the development of new muscle relaxants. During that time -

-or better yet, I should say we tried to develop a new reversal drug but did not succeed. Most certainly during that time, however, we did define an unmet medical need which I now will describe.

[Slide 12]

So, during this presentation I will first discuss the role of neuromuscular blocking drugs in general anesthesia; the current pharmacologic reversal of non-depolarizing neuromuscular blockade, which is predominantly neostigmine in the United States; and the need for an improved reversal drug.

[Slide 13]

First I would like to set the stage for the current use of neuromuscular blocking drugs. First, use of neuromuscular blocking drugs have two aspects. The first is to provide optimal facilitation of and conditions for successful endotracheal intubation, after which mechanical ventilatory support is possible. Secondly, it is to provide effective skeletal muscle relaxation in order for optimal surgical conditions to exist.

Historically, this relaxation was provided by the anesthetic a long time ago. Unfortunately, early on it was

realized that the dose of anesthetic required to produce both anesthesia and optimal surgical conditions often caused severe cardiovascular depression or problems. In the late >40s and >50s use of neuromuscular blocking drugs, initially d2-tubocurarine, a long time ago-Ballowed smaller doses of anesthetic to be delivered; created a more stable cardiovascular situation and still allowed production of maximal or optimal surgical conditions.

With regard to the second bullet point, the two above current uses of neuromuscular blocking drugs carry with them the risk of postoperative residual neuromuscular blockade or paralysis which dictates the necessity to provide pharmacologic reversal of neuromuscular blockade which, as I mentioned before, now is predominantly with neostigmine.

[Slide 14]

So the ideal reversal drug, one might say, should minimize the risk of residual paralysis. It should eliminate the side effects associated with neostigmine and muscarinic antagonists, and I will talk about that a little bit later. It should provide rapid reversal in minutes in a predictable fashion. It should enable the reversal of

profound neuromuscular blockade which will provide the possibility of flexible dosing of the neuromuscular blocking drug, and I will define what I mean by flexible dosing. Lastly, it should provide an alternative to succinylcholine in the form of a non-depolarizing neuromuscular block, like rocuronium that has a fast onset, and then we would be able to create a fast offset with the use of a new reversal drug. That would be ideal.

[Slide 15]

Now let's move to the postoperative period. Is postoperative neuromuscular block a real problem is what the question is. Current outcome analysis is to define critical specific patient care events.

[Slide 16]

So, in this case we will define critical respiratory events in the recovery room or the PACU as upper airway obstruction, inadequate ventilation, hypoxemia or a combination of those, and the incidence varies from 0.8 to 6.9 percent. I am now referring to the first 15-30 minutes upon entrance into the recovery room.

[Slide 17]

And so, why does this occur? Frequently it is

from residual neuromuscular block. It also can be caused or contributed to by the use of opioids, naturally for the use of pain relief, and is more common in patients with emergency surgery, long duration of surgery and abdominal surgery.

[Slide 18]

So, the incidence of residual paralysis from neuromuscular blockade remains a serious concern despite the current use of intermediate-acting neuromuscular blocking drugs and the administration of neostigmine.

[Slide 19]

Let's talk about current reversal of neuromuscular block. The only available products are acetylcholinesterase inhibitors of which, as I have mentioned before, neostigmine is the dominant one. Neostigmine has an indirect mechanism of action. It has the potential for allowing a postoperative reappearance of neuromuscular blockade and is associated with a wide variability in the time required for complete reversal of neuromuscular blockade.

To manage the side effects of neostigmine we must give another drug along with it, and that is co-administration of muscarinic antagonists, usually

glycopyrrolate. There are side effects to the muscarinic antagonists or the combination of neostigmine and the muscarinic antagonists or glycopyrrolate, and I am going to center on a couple of those in a little bit more detail in the next slide.

[Slide 20]

So, problems with the neostigmine/glycopyrrolate combination are, number one, it is ineffective in reversing in a predictable manner profound neuromuscular blockade. Cardiac arrhythmias occur, usually in the form of tachycardia or bradycardia, depending on one=s ability to properly match the neostigmine and the glycopyrrolate and the combination of two powerful cardiovascular drugs.

Is the combination that you happen to select correct for that individual patient? And, does the need to mechanically mix the drugs or give the two drugs so close apart introduce the opportunity for errors?

As president of the medical staff at the UCSF, we, and everybody else across the country, is centered on the need to reduce errors in medicine, and certainly the need to mechanically put two powerful drugs like that together is an opportunity we would like to avoid for errors to occur.

[Slide 21]

Now I am going to switch on you and talk about flexible dosing of neuromuscular blocking agents. Current reversal drugs, mainly neostigmine, are unable to reverse a profound neuromuscular blockade in a predictable manner and, therefore, may prevent flexible neuromuscular drug dosing. Yet, a profound neuromuscular blockade may provide better surgical conditions in certain situations. However, if one is worried about the efficacy of reversing a block with neostigmine, one then is very cautious in whether they should produce a profound neuromuscular block.

The second point is that a future drug should allow reversal in minutes from any depth of block, of course, which would allow then flexible dosing to occur.

Lastly on this slide, we should be able to continue the neuromuscular blockade until the end of the procedure and reverse as clinically needed. What happens now is that anesthesia care deliverers are a little bit hesitant about continuing an in-depth or a very deep block right to the end of the case because they are afraid they cannot reverse the block with neostigmine.

We could provide more optimal surgical conditions

if we could continue the block until the end of the procedure and then reverse the block in a predictable fashion. This would facilitate the surgeon closing the surgical wound in a more effective manner.

[Slide 22]

Now let's talk about an alternative to succinylcholine.

[Slide 23]

Most of you are well familiar with succinylcholine. It has many associated complications which include hyperkalemia. Succinylcholine is a trigger for malignant hyperthermia; occasional irreversible prolonged neuromuscular block in those patients whose enzymes may not be able to metabolize succinylcholine; cardiac arrhythmias; and also muscle pain.

So, in preventing muscle pain, which is probably the result to some degree from the vesiculations that are caused from succinylcholine when it is depolarizing the receptors and muscle membranes, and also the biochemical changes that may occur, especially in damaged muscles such as trauma, in association with succinylcholine administration.

[Slide 24]

In fact, succinylcholine has been used for over 50 years with its side effects. I would imagine that if the drugs were switched today and, in fact, you were now being presented with the challenge of removing succinylcholine for routine clinical use which, as you know, has a quick onset and a quick offset, I am sure you would reject it but, yet, we have been using it for 50 years, which I think dictates the need for a drug that can convert rocuronium from its quick onset and then, with a new reversal drug, have a quick offset and then be able to replace succinylcholine. I think that would be quite a desirable effect in medicine.

[Slide 25]

So, the medical need is for an improved reversal drug. An improved reversal drug should quickly and completely reverse neuromuscular block irrespective of the depth of blockade and without the need to manage the side effects of currently available reversal drugs, again, mainly neostigmine.

In combination with a fast onset neuromuscular blocking drug, an improved reversal drug may provide an alternative to succinylcholine and I believe that the

properties of an improved reversal drug will offer real and important patient benefits. Thank you very much.

[Slide 26]

Now that I have presented sort of the view of not having that drug, we are now going to start talking about sugammadex so next will be the discussion and presentation of the mechanism of action of sugammadex by Dr. Bom.

Mechanism of Action of Sugammadex

DR. BOM: Mr. Chairman, ladies and gentlemen, I will discuss the mechanism of action of sugammadex.

[Slide 27]

In my presentation I will show you how we designed sugammadex; how the mechanism of action of sugammadex actually works; the selectivity; the speed of reversal; and the pharmacokinetics of sugammadex; and an assessment of drug-drug interactions.

[Slide 28]

It is well-known that recovery from neuromuscular blockade is achieved by decrease in neuromuscular blocking concentration and this is done by two different ways, by metabolism and/or excretion. Also we have some recovery of the neuromuscular function. We can administer an

acetylcholinesterase inhibitor which will increase the acetylcholine concentration, resulting in a faster recovery.

[Slide 29]

In 1997 we discovered a new concept, the inactivation of the neuromuscular blocking agents, and this can be achieved by a rapid chemical interaction between the neuromuscular blocking agent and the encapsulating agent.

[Slide 30]

As a starting point for using encapsulating agents we decided to use cyclodextrins. Cyclodextrin has been used since 1953, a solubilizing agent, because it forms low affinity complexes at lipophilic drugs.

[Slide 31]

Here we see an example of gamma-cyclodextrin which is composed of eight sugar molecules in a ring, a very rigid molecule which cannot be broken down in your body. In the center we see a big cavity where lipophilic compounds prefer to stay.

[Slide 32]

Cyclodextrins are very water-soluble; are not metabolized in our body; and are renally excreted.

[Slide 33]

Here we see the structure of rocuronium. Rocuronium is a steroidal neuromuscular blocker. We see in the middle the steroidal nucleus, in yellow in this little diagram. Here is the morpholino group of rocuronium, as indicated in this diagram in gray, and here we see the positively charged nitrogen of the molecule that I indicated here in this simplified diagram with a plus sign.

[Slide 34]

So, when we bring rocuronium together with gamma-cyclodextrin the steroidal part of rocuronium, which is lipophilic, prefers to enter the cyclodextrin but it is very clear from this drawing that the cavity of the cyclodextrin is not big enough to encapsulate the whole steroidal parts. So, we decided to put on each sugar molecule a side chain that extends the cavity, and to make the affinity even better we decided to put negatively charged end groups of the side chains that will hold this positively charged molecule in a fixed position in relation to the cyclodextrin molecule.

[Slide 35]

Well, after synthesizing approximately 40 compounds, we discovered sugammadex. Sugammadex is a gamma-

cyclodextrin of eight sugars in the ring. You see the eight side chains and at the end of the side chains you have a carboxyethyl group which is negatively charged.

[Slide 36]

We were also lucky that we were able to make complexes of rocuronium and sugammadex and crystalized them. That allows x-ray crystallography so you can really see the true confirmation between the two molecules and how they interact. You see here the morpholino group of rocuronium. This is the steroidal part of rocuronium, nicely wrapped up inside this gamma-cyclodextrin ring and a part of the side chains. Here we can just spot the positively charged nitrogen which is held in a fixed position, all these negatively charged end groups.

[Slide 37]

So, what happens when the rocuronium molecule encounters an empty sugammadex molecule? Well, they form a very tight complex. It is not a chemical action but it is a chemical interaction. That means that molecules can form a complex but they can also leave the complex. But due to the high affinity, the chances of binding are 25 million times higher than the chances of leaving.

We can see at the bottom of this slide that by modifying gamma-cyclodextrin into sugammadex the affinity of rocuronium and vecuronium for sugammadex improves dramatically so it is really enhanced binding that we create by modifying this molecule.

[Slide 38]

Well, what is the selectivity of sugammadex? Well, sugammadex was specifically designed for steroidal neuromuscular blocking agents so it is no surprise that we see high affinity for these agents, whereas the non-steroidal blockers, like cisatracurium have very poor or no binding at all to sugammadex.

[Slide 39]

How can we explain the very fast reversal that we see with sugammadex? When rocuronium is injected into the circulation and is circulating in the blood vessels it will rapidly start to diffuse in extracellular volume, as we can see on this slide.

[Slide 40]

We get a very rapid equilibrium that explains the very fast onset of rocuronium.

[Slide 41]

When we then inject sugammadex all the rocuronium molecules inside the blood vessel will be encapsulated so the free rocuronium concentration in plasma will be close to zero and that is a gradient between the high concentration in the extracellular volume and the concentration close to zero in the blood vessel.

[Slide 42]

As a result, rocuronium molecules will rapidly move from the extracellular volume into the blood vessel.

[Slide 43]

We now look at what happens when we inject sugammadex and we just look at sugammadex alone.

[Slide 44]

First we see it appearing in the bloodstream as sugammadex will also rapidly start to diffuse into the extracellular volume. So, we see now two effects happening simultaneously. You see there is opposite direction of the flow of the molecules.

[Slide 45]

Sugammadex molecules are rapidly entering the tissue while rocuronium molecules are rapidly moving toward a blood vessel. This means that these molecules will

encounter each other very quickly, and as soon as they meet each other they form a very tight complex.

[Slide 46]

To conclude, sugammadex rapidly encapsulates rocuronium and vecuronium. This allows reversal of any depth of neuromuscular blockade, including the profound blockades. And, sugammadex is inactive against non-steroidal neuromuscular blocking agents like succinylcholine and cisatracurium.

[Slide 47]

In the second part of my presentation I want to discuss the pharmacokinetics and the drug-drug interactions.

[Slide 48]

You see the basic pharmacokinetic data of sugammadex. There is a volume of distribution of 12-15 liters, or more or less the extracellular volume. The plasma half-life is 2.2 hours. The clearance is 91 ml/minute, which is approximately the glomerular filtration rate, and there is no metabolism of sugammadex at all.

[Slide 49]

Furthermore, there is fairly low plasma protein binding and studies in animals have demonstrated that the

blood-brain barrier penetration is very poor, less than three percent in the rats, and also that the placental transfer is limited, less than two to six percent in rats and rabbits.

[Slide 50]

Here we see a plasma concentration time plot of both rocuronium and sugammadex. At time zero we inject a normal intubation dose of 0.6 mg/kg of rocuronium. We get a rapid rise of concentration in plasma, followed by an exponential decaying in concentration. When the second twitch of the Train-of-Four reappeared we injected 2 mg/kg of sugammadex. You see again a rapid rise of sugammadex followed by an exponential decay.

It is important to see in this slide that during the following eight hours the concentration of sugammadex is always exceeding the concentration of rocuronium. This means that when the complex has formed and a molecule would escape there would be plenty of empty cyclodextrin molecules waiting to immediately encapsulate an escaping rocuronium molecule, and this ensures that we maintain complete reversal.

[Slide 51]

In the next part I will discuss the evaluation of the potential drug-drug interactions. Sugammadex has been specifically designed to form very high affinity complexes with the steroidal neuromuscular blocking agents rocuronium and vecuronium. Sugammadex is almost exclusively renally excreted. Sugammadex has no potential to cause drug-drug interactions due to inhibition or induction of drug metabolizing enzymes. And, the mechanism of potential drug-drug interaction is through binding of sugammadex to other compounds, which cannot be assessed by traditional studies.

[Slide 52]

There are two different types of binding that can happen. We can have displacement or we can have capturing. Let me start with displacement. When sugammadex has formed a complex with a neuromuscular blocking agent and we add a third compound that is able to displace rocuronium or vecuronium from the complex with sugammadex, we get an increase in free rocuronium concentrations or vecuronium concentrations and we have a potential risk of reoccurrence of neuromuscular block.

But capturing is a slightly different issue. If sugammadex is administered and could potentially bind to

another drug, thereby decreasing its effective concentration, that would result in reduction in efficacy.

[Slide 53]

So, how did we address this problem with different approaches? First we determined the affinity of drugs for sugammadex by using a technique called isothermal titration microcalorimetry. Once we knew the affinity of the drug we could estimate, from in vitro and in vivo studies, how the affinity data relate to the biological effect. We also used a pharmacokinetic/pharmacodynamic interaction model that we can use to predict if in a clinical situation there will be an interaction. We also took clinical considerations into account.

[Slide 54]

Since it is impossible to test all known drugs to man because that would be an endless job, we decided to select certain groups of drugs which are the most relevant. Of course, if sugammadex is used for the reversal of neuromuscular block direct use in anesthesia was a top priority. Secondly, since sugammadex was designed to encapsulate steroidal neuromuscular blocking agents we, of course, were interested in the affinity of drugs or hormones

with a steroidal nucleus to see how they bind to sugammadex. Also, molecules that are not steroidal but can take a three-dimensional configuration which allows them to act on steroidal receptors that are also potential candidates is the third category. Of course, we looked at drugs most commonly prescribed because most of your patients will have exposure to them. We tested more than 300 compounds using this approach.

[Slide 55]

Of all the drugs in anesthesia that we tested, we found that remifentanil was the one with the highest affinity, but this was only 0.2 percent of the affinity of sugammadex for rocuronium.

[Slide 56]

We also used a very conservative scenario to evaluate these drug-drug interactions because we only assumed that a drug would interact with sugammadex and neuromuscular blocking agents would interact with sugammadex. What we don=t take into account is that drugs, of course, have a very high affinity for their receptors that also bind to all kind of proteins both in the blood and the tissue. Mostly, to a large fraction, they are bound to

albumin and for certain drugs they have very high affinity for specific transporter proteins like transcortin or sex hormone binding globulin.

[Slide 57]

So, we identified three drugs with a potential displacement issue. There was toremifene, which is an orally administered non-steroidal selective estrogen receptor modulator used for the treatment of metastatic breast cancer. The second candidate was flucloxacillin, which is a narrow spectrum beta-lactam penicillin but this drug is not available in the United States. We also identified fusidic acid, which is a steroidal bacteriostatic agent also not available in the U.S.

[Slide 58]

For hormonal contraceptives a clinical relevant capturing interaction could not be excluded, and progestogens and estrogens show some affinity for sugammadex, in the range of 2-22 percent of that of rocuronium. But in preclinical animal studies, in doses up to 500 mg/kg/day, we never saw any interaction suggesting that there was an effect for the induction of steroidal hormones.

[Slide 59]

A conservative pharmacokinetic simulation predicted a decrease of 34 percent in unbound progestogen exposure. This decreased exposure is similar to the situation in which an oral contraceptive is taken more than 12 hours too late, and guidance will, of course, be provided in the package insert.

[Slide 60]

So, in conclusion, the affinity constants for more than 300 compounds tested confirmed the highest affinity for steroidal and steroidal-like compounds. For the compounds discussed, the available data suggest that an interaction cannot be excluded, and this will be addressed in the package insert. But, most importantly, no clinical evidence of interactions was found during clinical trials in approximately 2,000 patients.

[Slide 61]

I would now like to give the word to Dr. van Den Dobbelsteen.

Nonclinical Safety Overview

DR. VAN DEN DOBBELSTEEN: Thank you, Ton. I will have the honor today to guide you through our nonclinical

safety data, and particularly with emphasis on data that can help address question two in your briefing document.

[Slide 62]

First of all, I would like to point out that sugammadex=s nonclinical safety profile is very comparable to that of modern cyclodextrins often used intravenously in various kinds of excipients but typically the dose that we use is significantly lower, like 10-34 lower, and, in addition to that, sugammadex is only meant for single dose use, where these other cyclodextrins are mainly used during repeated dosing regimens.

[Slide 63]

During my presentation I will be using safety margins to express basically the drug concentration at the no observed effect level in rat versus the concentration at the clinical dose in humans. In that case I will refer to the clinical dose that will probably be most used in the clinic, 4 mg/kg. I want to talk about concentration. I will be talking about local concentration if I am addressing effects on bone and teeth and I will be talking about systemic exposure, AUC or peak plasma concentrations, regarding potential target organ systems.

[Slide 64]

First of all general nonclinical safety data. Sugammadex has no intrinsic pharmacological activity; no genotoxicity; no relevant reproductive toxicity; no teratogenicity; and only at the very high or repeated doses the typical organs for cyclodextrins will show initial histopathological effects. However, we have established fairly wide safety margins, like over 25 and to put it into reference for what most of you anesthesiologists have been using in the surgical theater, mostly the compounds that you are using are associated with a safety margin between 5-10 at most.

There is one observation that might be specific to the cyclodextrin, and that is its binding to mineralized tissues such as bone and teeth. However, we have established that this basically does not represent a risk to man, and why is that?

[Slide 65]

In all of the preclinical work that we have done we have established a very large safety margin between rat and human. Looking at the effects on bone, our safety margin basically ranges from 70-1,000, and if we look at the

effects that we observed in the juvenile rat molar model, dosed for four weeks repeatedly, 500 mg/kg, we have been able to establish safety margins of 48 to probably close to 500.

The fact that we don=t see any effect on bone development or ossification in the embryofetal development studies and in our juvenile animal studies provides us very important information with respect to the risk of the pediatric population and we can conclude from all of this nonclinical, fetal and juvenile animal data that there is basically no risk. In addition to that, there is no expected risk for impairment of fracture, would it occur prior to surgery or would have good bones after being damaged inter-surgically.

[Slide 66]

As I said, we have done an extensive set of bone and teeth investigation studies, altogether 15, and many of the protocols have been in agreement with the FDA and NMBA agency before we initiated particular studies. For the studies on the young adult rat model and juvenile rat model, I wish to point out that these models are very sensitive as compared to the human, and why that is I will point out

later.

As I pointed out, the embryofetal development studies that we have done basically cover processes that are important for healing because the same processes that are ongoing during embryology play an important role during bone healing.

Drug deposition studies, we have basically established and characterized the exact localization of sugammadex in bone. We have looked at the reversibility of binding, and also quantified the binding to basically get a better risk assessment. Very important for the clinical situation, we have also looked at the prevention of binding of sugammadex to bone by rocuronium because that is basically what you will be doing in the clinic.

[Slide 67]

This slide gives you an overview of all the different methodologies that we have used in addressing potential effects on tooth color and development and also in assessing the effects of the compound on bone structure, quality, turnover, growth and development, modeling and remodeling.

[Slide 68]

First of all, the results of drug disposition studies. Sugammadex=s binding is reversible after an initial half-life of, like, three weeks and a slower phase in which the compound wears off bone again. Binding to teeth is significantly less as compared to the binding to bone, and the most likely binding site has been established to be hydroxy apatite. Very importantly for the clinical situation, the presence of the NMBA does reduce the binding of sugammadex to bone by a factor of two. Very important, if we look at the juvenile animal models or other human models for example on bone growth, sugammadex does not bind to the epiphyseal disc and, therefore, should not impair normal growth. And, bone apposition continues normally as sugammadex is deposited to bone so that also tells you that this compound does not intoxicate cells and processes that are important to normal bone physiology.

[Slide 69]

This slide is very important to point out to you the sensitivity that we have in our nonclinical models. On your left-hand side you can see the extent of bone binding to juvenile rat bones in comparison to young adult rats and in comparison to old rats that basically have very slow

growth. So, this slide basically indicates that in the juvenile animal model that we have been using a large fraction of the dose is being absorbed in bone. If you compare it, for example, to the young adult or to the old rat this is almost negligible. The same is actually true for teeth.

So, the rate of bone turnover really determines how much sugammadex is being incorporated into bone and, therefore, we can conclude that the juvenile rat model and also the young adult rat model that we used are very sensitive to these effects.

How about inter-species extrapolation? For that you have to go to the right-hand side of the graph. You see that all of the dose that is not being recovered in the rat is like 15 percent of its radioactivity. If you compare it to man, that is three-fold less so the incorporation in the human adult is much less. So, this basically emphasizes the very high sensitivity of our model.

Based on this human recovery data we have been able to establish a worst-case estimate of a maximum concentration of sugammadex in bone that will ever be reached at the dose of 4 mg/kg to be 4.5 Φg/gram. Please

remember that figure because that is the way I will express my safety margins.

[Slide 70]

Let=s turn to the young adult rat model. We basically don=t see any adverse effects at the single dose up to 500 mg/kg, and the associated concentration with that dose is 313. So, there we derive a safety margin of 70 and this is a very conservative estimate.

In addition to that, we have done traditional four-week toxicity studies where you really get an accumulation of the compound if the bone is really a worst-case situation, and by traditional histopathology we are also at bone marrow density and basically we did not see any effect. The resulting safety margin is far over 1,000.

[Slide 71]

Now let=s turn to the juvenile rat model and basically look at a very important parameter, namely growth. Basically, you see over here that sugammadex up to the dose of 500 mg/kg, given for four weeks, does not impair growth. So, that basically, based against the human estimate of 4.5 Φg/gram, gives us again a fairly wide safety margin. Speaking as a toxicologist with ten years of experience,

these safety margins are really unprecedented.

[Slide 72]

Now let=s turn to the teeth. As I already indicated, in our adult rat model and in our dog model we don=t see any effect on teeth discoloration. In the juvenile rat we don=t see any teeth discoloration after a single dose of 550 mg/kg, based on local exposure a safety margin of 48.

Even in molars in rats we looked at histopathological effects on the molars and we don=t see any effect up to a dose of 120 mg/kg given for four weeks. So, if you would calculate that by accumulated dose you would end up with a dose like 3,360 mg/kg. Please compare that in your mind to the proposed clinical dose that we are using. But also on local exposure we have an extremely wide safety margin. The effect that we see in the rat model is observed at 500 mg/kg but the effect that we are actually observing is just about to be an effect because initially the effect is still reversible after an eight-week withdrawal period.

I do wish to point out that the rat model is anatomically the most representative for the human case as the rat is very oversensitive, and that has been well

described in the literature.

[Slide 73]

Now let=s translate all of these data into risk assessment for the human pediatric population. We see basically no effects on bone. We do see an effect on tooth development but with a very wide safety margin, and also the other potential target organs have been addressed in a toxicity study with a significant safety margin. So, basically based on all this we can conclude that there should be no specific risk for pediatric populations under the proposed conditions of clinical use.

[Slide 74]

Now let=s turn to an even earlier life stage, the embryo, and assess the potential risk for the embryofetal development studies and how we assess from that the absence of risk for fetal development for human fetal development. We observed no basic effects on the human skeletal development and ossification, and we also specifically designed studies to estimate skeletal exposure ongoing during embryogenesis in the rat and found the figures to be in several hundreds.

Again, putting that in perspective to the worst-

case human estimate of 4.5 Φg/gram, you end up with a safety margin of over 100.

I do wish to point out, however, that placental transfer in the human situation will probably also be low, very low, and that has not been taken into account for the safety margin. So, if we would assume a placental transfer of approximately 10 percent this safety margin would have to go up by a factor of 10. Therefore, given this very conservative approach that we have taken, there is no risk expected with respect to the human fetus.

[Slide 75]

Now, this data that we have produced is also very important for assessing potential risk for impaired fracture impairment because, as I said, the processes that are important for skeletal tissue formation in utero are very similar processes that are important for bone healing. So, by extrapolating and doing a very conservative risk assessment based on this model, we have actually been able to actually conclude that fracture healing should not be impaired.

Also, in all of these other processes we have been studying in our dedicated bone toxicity studies in the young

adult model basically we see no toxicity to bone and no function impairment, with safety margins, as I already indicated, between 70-1,000.

Another important point to bring out is that sugammadex has no intrinsic pharmacological activity and compounds that have been associated with impaired bone healing actually do bind to bone or related tissues but, in addition to that, do have pharmacologic activity which causes disturbance of bone healing.

Typically in the surgical situation you would administer sugammadex, like, at the end of the case and bone mineralization in a callus only starts to occur two or three weeks after bone fracture. So, increased binding to bone, and particularly to callus, would not be expected. So, based on all this evidence we can basically conclude that fracture healing should not be impaired.

[Slide 76]

That brings me to the end of my presentation and, hopefully, I have convinced you that sugammadex=s nonclinical safety profile shows very wide safety margins relative to human exposure, like I said, almost unprecedented.

We have done an extensive set of 15 nonclinical safety studies, some in consultation with the various agencies around the world, and we have really characterized the risks of the binding to mineralized tissues. As I have also pointed out, these nonclinical models are very relevant and very sensitive.

[Slide 77]

Nevertheless, we have had enormous safety margins, conservatively estimated, for the effects on bone and teeth and based on these very wide margins we can basically conclude that there should be no risk, particularly given that in clinical use sugammadex will always be used in combination with rocuronium and vecuronium and binding will even be further reduced, and that is not taken into account in these conservative estimates of safety margins that we have.

So, basically given all of this evaluation, this addresses not only that use in the normal patient would be safe but also in the very sensitive patients such as patients undergoing fractures that have to heal, the unborn child, the pediatric population and patients potentially having to use sugammadex in a repeated dose manner.

So, altogether we can conclude that at clinical exposure levels there is basically no nonclinical safety data that suggests any adverse effects for any target organ for all life stages.

[Slide 78]

That brings me to the next presenter of this presentation, who will be Patrick Boen who will guide you through the efficacy highlights.

Efficacy and Safety Clinical Overview

DR. BOEN: Thank you, Dr. van Den Dobbelsteen. Although I will be speaking about efficacy, I think it is important to note that sugammadex performance is all about safety. It is not intended to treat an illness; it is not intended to treat a condition. Its sole intention is to undo the effects of muscle relaxants, and these muscle relaxants are much needed during surgery but can be dangerous and even life-threatening at other moments. So, with that in mind, let=s see how sugammadex performs.

[Slide 79]

Now, what I would like to do is to go over the goals of the clinical development program; talk about the program standards; the inclusion and exclusion criteria; the

neuromuscular monitoring that we employed during the trials; the dose-finding trials in Phase II; the Phase III clinical trial program; and the efficacy conclusions.

[Slide 80]

Already from the onset, once we knew that the mechanism of action was different from what is available right now, we wanted to go and investigate three different situations. routine reversal, shallow blockade where reversal would take place at reappearance of the second twitch, but also profound blockade reversal at the reappearance of 1-2 post-tetanic counts; and the last one, immediate reversal, reversal at 3 minutes after a very high dose of rocuronium.

[Slide 81]

Now, I am not going to go over all these studies, but this is just to give you an idea about the comprehensiveness of this program. We did 30 clinical trials in Phase I, II and III. This is 1,973 subjects divided over Phase I, II and III, and I think that is quite an accomplishment.

[Slide 82]

The inclusion criteria: Patients were to be off

ASA class 1 or 2 or 3 or 4 depending on the trial. They had to be adult patients, except for trial 19.4.306 which was a pediatric trial performed in Europe, undergoing general anesthesia requiring an NMBA. Surgical procedures were to be in the supine position and, of course, patients would have given informed consent.

[Slide 83]

The exclusion criteria were neuromuscular disorders; significant renal dysfunction, except for one specific trial where we did studies in patients with renal dysfunction; history of malignant hyperthermia; allergy to narcotics, muscle relaxants or other medication used during general anesthesia; furthermore, medications known to interfere with the NMBA; contraindications for the comparator--

[Slide 84]

--and pregnancy, childbearing potential or not using appropriate methods of birth control and breast-feeding women. Prior participation in the trial was also not allowed, and participation in another clinical trial which was not pre-approved by our company was not allowed.

[Slide 85]

Now, over the whole program we used a neuromuscular monitoring device. We call it the TOFwatch which is based on AMG, or acceleromyography, which basically provides stimuli at the ulnar nerve and measures muscle accelerometry at the thumb.

[Slide 86]

Most of you already know this, but this is how the Train-of-Four works and post-tetanic counts are actually conducted. This is how it works. You give a stimulation of four electrical stimuli. You wait and after that you see one to four responses. In this case, in the last picture you see four responses and you see that the fourth response is only slightly lower than the first response. In this case, the Train-of-Four ratio is approximately 0.8, 0.9. Now, in the first two pictures there is not even a fourth response so, by definition, the Train-of-Four ratio there is zero.

Now, this measurement of neuromuscular blockade is primarily used when more shallow blockade is being measured. When more deeper blockades are being measured post-tetanic count is being used. Post-tetanic count is done as follows. We give a 50 Hz tetanic stimulation during five, six

seconds. Then we wait three to five seconds and then we give single twitches at a slow rate and then count the following twitches. Now, that can be one, that can be two. In this case there are two twitches; in this case there are four twitches. So, the result here is a PTC of 2 and the result here is a PTC of 4.

[Slide 87]

Let=s go to the dose-finding studies.

[Slide 88]

Now, in finding our doses for Phase III we had a couple of dose selection criteria. First of all, we wanted to minimize the risk for inadequate recovery but also we felt that we needed to go for a clinically significant reduction in recovery time. And, we defined that, together with our clinical experts as less than five minutes. Also, we wanted to minimize the potential for confusion in dosing. That means that we had to refer a limited choice of recommended doses for the Phase III program.

[Slide 89]

Here you see the first results for a shallow block situation. This is the time axis. The Y axis is the time or the median time to recovery to a Train-of-Four of 0.9 and

in this case after a placebo dose, so after placebo time to recovery takes about 50 minutes. With increasing doses of sugammadex, 0.5, 1, 2, 3, 4, 5 and 6, you see an increasing effect leading to a decrease of the median time to recovery.

If we then zoom into the doses of interest, you see that after approximately 2 mg/kg of sugammadex there is no appreciable reduction in time to recovery anymore. This is the situation where sugammadex was tested at the reappearance of T_2 after rocuronium at a dose of 0,6 mg/kg.

[Slide 90]

A similar graph I can show you here for vecuronium. Again, if we immediately go to the inset we see that the dose of interest, 2 mg/kg, gives a reversal time which is approximately three minutes, a little lower than three minutes, and increasing the dose to 4 mg/kg does not give an appreciable further reduction in recovery time.

[Slide 91]

The profound block situation and, remember, profound block means that we now give sugammadex at a depth of 1-2 PTC so the depth of the blockade is much deeper. We are going to the doses of interest again. Here you see that it is more difficult to return the level of blockade and,

indeed, you need 4 mg/kg to come to a reversal time of about two minutes.

[Slide 92]

Going to the vecuronium data, again here for the same situation, profound block, 4 mg/kg does the job.

[Slide 93]

Now, in an immediate reversal situation the criteria are somewhat different. If you are in dire need to reverse a patient, then seconds may count and in that case the small differences between 12 and 16 may actually be very relevant.

[Slide 94]

That is why we have chosen for our Phase III studies that the following doses would be investigated. So, these doses were to be investigated, 2 mg/kg at the reappearance of T_2, 4 mg/kg at 1-2 PTC or at 15 minutes after rocuronium or vecuronium, 16 mg/kg for immediate reversal after 1.2 mg/kg rocuronium. And, what we further found during our dose-finding studies was that there was a clear dose-related speed of recovery, the more you give, the faster it works; that there is a clear dose-related reversal of the depth of neuromuscular blockade, the more you give

the deeper the block you can reverse.

[Slide 95]

In Phase III we did quite a few studies. The comparative studies were against neostigmine, both in shallow block and in profound block, versus succinylcholine, versus cisatracurim. We also did a routine use study where the only requirement was to have sugammadex to be administered at least 15 minutes after the last administration of rocuronium, so more or less mimicking a clinical situation.

[Slide 96]

Also special population studies were performed, the 304 study, the renal study and I already mentioned that study. We did a study in geriatric patients, a study in pulmonary patients and a study in cardiac patients.

[Slide 97]

First I would like to discuss the comparative studies with neostigmine, the 301 and the 302 studies. The objectives of these studies were to show that reversal of shallow or profound rocuronium- and vecuronium-induced blockade with sugammadex was faster than with neostigmine.

[Slide 98]

Here you see the results. In this first column you see the sugammadex results. In the second column you see the neostigmine results. In this first row you see the rocuronium results and in the second row you see the vecuronium results. It is very clear that the median time to reversal with, in this case, rocuronium of 1.4 minutes is vastly superior to that of neostigmine which takes about 17.6. The same is true for vecuronium, 2.1 versus 18.9 and, of course, this is highly, highly statistically significant.

[Slide 99]

Another way of looking at that is with a time-to-event graph. What you see here is on the left axis, the Y axis, is the percentage of patients returning to a Train-of-Four of 0.9 over time. On the X axis obviously you have the time. What you see is that there is very steep curve for both rocuronium and vecuronium in the sugammadex group and there is a much less steep curve for rocuronium and vecuronium in the neo group. And, you could say that within approximately 10 minutes the majority, more than 90 percent of patients, on sugammadex have already returned to a Train-of-Four of 0.9 and at that point in time the first patients

who received neostigmine are starting to recover.

[Slide 100]

The second study, the 302 study, went for profound blockade. Again, profound blockade is defined as reversal at a time point where 1-2 PTCs were found. Here there are very consistent results. For rocuronium we find a reversal time of approximately 3 minutes and for neostigmine about 50 minutes; for vecuronium 3.3 minutes, for neostigmine almost 50 minutes, or a factor of about 17 times faster.

[Slide 101]

Looking at the time-to-event curve, this curve is probably even more dramatic because if you look at the first patient on rocuronium who returns with neostigmine, at that point in time virtually all patients on sugammadex have already returned to 100 percentB-sorry, to 0.9 Train-of-Four.

The same is true if you look at the vecuronium patients. The first patient who returns with vecuronium and neostigmine comes back at a point in time where more than 90 percent of the patients who received vecuronium and sugammadex have returned.

[Slide 102]

So our conclusions as far as these two trials are concerned are that there is faster recovery compared with neostigmine after rocuronium- and vecuronium-induced block; no cases of residual paralysis or reoccurrence of blockade during the period of neuromuscular monitoring or at recovery; and, thus, there is unique ability to rapidly reverse both shallow as well as profound rocuronium and vecuronium-induced blockade.

[Slide 103]

Now I would like to discuss trial 303, and trial 303 is an important trial because I also believe that the FDA have some questions about this trial with respect to the immediate reversal. I will take a couple of slides to explain the background of the study and to explain the results of the study, and even after the presentation during the Q&A session we are quite willing to address questions on this particular study.

The objective of this study was to show that reversal of profound rocuronium-induced neuromuscular block with sugammadex is significantly faster than recovery with succinylcholine.

[Slide 104]

The primary efficacy variable was the time from the start of administration of rocuronium or succinylcholine to recovery of a T_1 to 10 percent. The secondary efficacy variable was time from the start of administration of rocuronium or succinylcholine to recovery of T_1 to 90 percent and clinical signs of recovery.

[Slide 105]

Now, there are a couple of design elements that are important in this study. First of all, a study in emergency patients just is not possible. It is because of ethical considerations but also because of enrollment issues. True emergency patients, true Acannot intubate/ cannot ventilate@ patients are very rare and it would be impossible to set up a study within a period of several years to conduct such a study.

In the study we used a high dose of rocuronium, the highest dose that is allowed for rapid sequence induction. The primary and the secondary efficacy variables, T_1 to 10 percent and T_1 to 90 percent, actually together allow for comparison of a full recovery profile. Furthermore, the T_1 of 10 percent at the thumb where we measured corresponds to approximately 25 percent at the

diaphragm, and that corresponds approximately to the first attempts of a patient starting to breathe.

Last but not least, we did reversal at three minutes because that would include 60-90 seconds of onset time for the neuromuscular blocker, leaving approximately 90-120 seconds for two intubation attempts and that was felt to be reasonable.

[Slide 106]

So the study looked like this. Patients were randomized. Fifty-seven patients went into the rocuronium group; 58 patients went into the succinylcholine group. The patients in the succinylcholine group were allowed to spontaneously recover then time to recovery to a T_1 of 10 percent was measured and time to recovery T_1 of 90 percent was measured.

In the rocuronium group, three minutes after rocuronium/sugammadex at a dose of 16 mg/kg was given, then time to recovery to T_1 10 was measured and time to recovery to T_1 90 percent was measured.

[Slide 107]

Let=s look at the results. Here you see the results. On the left-hand axis, the Y axis, you see the

time that it took to come to these different endpoints. The two left columns show the time to a T_1 to 10 percent. The most left column is rocuronium together, the combination with sugammadex, and the blue column indicates succinylcholine.

You already can see that the combination of rocuronium and sugammadex is statistically significantly faster in obtaining a T_1 to 10 percent than succinylcholine, but the remarkable thing here is also that if you look at the T_1 to 90 percent, actually if you look at the combination of rocuronium and sugammadex it is actually faster in obtaining a T_1 to 90 percent than succinylcholine is in obtaining a T_1 to 10 percent.

[Slide 108]

Another way of looking at it is with this graph. Here we have all subjects plotted out with T_1 values and T_9 and you can see the individual evolution of each and every patient. Now, one of these patients has been marked succinylcholine because this is an intent-to-treat group and by accident this patient received succinylcholine. So, this is the rocuronium and sugammadex group whereas this is the succinylcholine group, and this patient was supposed to be

in this group. You can see the dramatic differences, and I have drawn a line at about eight minutes because that is the line where arguably one could start to lose some brain function.

[Slide 109]

So, our conclusion with regard to trial 19.4.303, the direct head-to-head comparison to succinylcholine, was that reversal of profound rocuronium-induced neuromuscular blockade with sugammadex was significantly faster than spontaneous recovery from succinylcholine and sugammadex, therefore, offers the possibility of immediate reversal of rocuronium-induced block in a possible scenario of a failed intubation.

[Slide 110]

We also did a comparative study with cisatracurium and neostigmine. The objective here was to show faster recovery from neuromuscular blockade with sugammadex after rocuronium than with neostigmine after cisatracurium. Again, very consistent results. The median time to recovery is 1.9 minutes, whereas for cisatracurium and neostigmine it is about 7.2.

[Slide 111]

Looking at the time-to-event graph, I think the picture is clear. At the moment the cisatracurium and neostigmine patients are starting to recover the majority of the patients on rocuronium and sugammadex have already reached a Train-of-Four of 0.9.

[Slide 112]

The other study I mentioned, the study where the only requirement was that sugammadex was given at least 15 minutes after the last administration of rocuronium, gives the following results. We did quite a few patients in this study, almost 180 patients, but again, very consistent results with a median time to recovery a Train-of-Four of 0.9 of 1.8 minutes.

[Slide 113]

So conclusions for these two trials: Reversal was significantly faster than neostigmine reversed cisatracurium-induced neuromuscular block, and sugammadex is also efficacious when administered at least 15 minutes after the last dose of rocuronium.

[Slide 114]

There were a couple of special population trials and I would like to share the efficacy results with you as

well. The trials that we did were renally impaired subjects versus healthy subjects, adult and geriatric subjects, and subjects with pulmonary and cardiac risk factors.

[Slide 115]

Here are the results. What you see here is that the median time to recovery in impaired renal function, patients with a creatinine clearance of less than 30 ml, is actually similar to patients with normal renal function, with a clearance of more than 80 ml/minute. That shows that the reversal really is not dependent on the organs. The compound is cleared completely by the kidney but the reversal itself is not dependent on the kidney.

[Slide 116]

Here you see the results for the geriatrics trial where we compared with a younger adult population. The interesting thing here is that there does seem to be a trend towards a longer recovery with older patients, and that is most probably explained by the fact that older patients have a longer circulation time. The compound needs to get there.

[Slide 117]

The pulmonary and cardiac risk factors: In these studies we did both 2 mg and 4 mg of sugammadex but again we

see very consistent results, with recovery times around 2 minutes, 1.9 and, in the cardiac study 1.7 and 1.3, and compare that to the placebo group where we had 34.7 minutes to recovery of 0.9.

[Slide 118]

So conclusions as far as the special population trials are concerned: Rapid and complete recovery from rocuronium-induced neuromuscular blockade in normal and renally impaired patients; both the 2 mg/kg and the 4 mg/kg doses were efficacious in pulmonary and cardiac patients; and there was no clinical evidence of residual neuromuscular or reoccurrence of blockade in these patients.

[Slide 119]

Overall conclusions for efficacy: There is a clear dose response. There is consistent efficacy over all trials. There is much faster recovery with sugammadex as compared to neostigmine. And, there are no dose adjustments necessary in special patient populations.

[Slide 120]

Now I would like to move over to the safety summary.

[Slide 121]

What I would like to do there is to give you some background information on the data sets, the demographics, the exposure to sugammadex and special population studies, then go into the safety data per se, the AEs, the SAEs, discuss specific AEs, some other safety parameters and laboratory changes.

[Slide 122]

Now we look at demographics. Age and age distribution between placebo groups and the total sugammadex groups was quite comparable. As far as gender is concerned, there were slightly more males in the placebo group than in the sugammadex group but only to a small extent.

[Slide 123]

In total, sugammadex was administered in 1,509 patients who also received rocuronium and in 398 patients who also received vecuronium. Furthermore, there were 443 exposures of sugammadex only in 196 subjects. So, these subjects received multiple administrations.

[Slide 124]

If we look at special populations, we identified several special populations in our data set-Bcardiac impaired, renal impaired, pulmonary impaired and hepatically

impaired. For the cardiac impaired, renal impaired and pulmonary impaired we also had special studies. That was not the case for the hepatic impaired but for these patients we had at least 77 patients in the total data set.

[Slide 125]

Looking at ASA classification, the majority of cases were from ASA 1 and ASA 2, more than 40 percent in both groups; a little more than 12 percent in ASA 3 and we had one patient in ASA 4.

[Slide 126]

The data sets that were used for safety evaluation were all clinical trials obviously. Then there was the pooled Phase I-III data set; the pooled Phase I data set and, breaking down from the pooled Phase I-III data set also sugammadex versus neostigmine data set and the sugammadex versus placebo data set.

[Slide 127]

A special population study which is worth noting is the healthy volunteer crossover trial, trial 19.4.106, where we had 12 patients completed and randomized to placebo or sugammadex at doses of 32 mg/kg, 64 mg/kg and or 96 mg/kg. Please note that sugammadex up to doses of 96 mg/kg

was safe and well tolerated. So, that really represents a very wide safety margin, and even if you look at the highest dose that we propose, the 16 mg/kg dose, that would be six times the dose in such an immediate reversal situation.

[Slide 128]

We did a study, as I mentioned a couple of times before, in renally impaired patients, 15 subjects with creatinine clearance of less than 30 ml/minute, 15 subjects with creatinine clearance of more than 80 ml/minute. Each patient received a dose of 2 mg/kg of sugammadex at the reappearance of the second twitch.

The patients were followed up for 2-4 weeks and the safety profile in these patients was actually not appreciably different from the control subjects. However, the clearance in these patients was about 17-fold reduced in severe renal failure and, therefore, as a measure of caution we recommend that in these patients the use of sugammadex would be strongly discouraged.

[Slide 129]

We also had two studies in cardiac impaired patients and in pulmonary complication patients, and there we found that use of sugammadex was safe and effective in

these populations.

[Slide 130]

There were two bronchospasms found. Two cases were reported as SAEs in asthmatic patients and they were considered possibly related by the investigator. One of these bronchospasms was shortly after reversal, around the time of extubation, and was successfully treated with terbutaline. The other bronchospasm was approximately one hour after reversal so approximately one hour after introduction of sugammadex, close to the time of extubation again, and that bronchospasm was treated successfully with albuterol.

[Slide 131]

Moving to the AEs and the serious adverse events--

[Slide 132]

-Bif we compare sugammadex and placebo and look at the number and incidence of subjects with at least one AE, we see that the incidences are quite comparable and possibly even a little bit better for sugammadex.

[Slide 133]

The most frequently reported adverse events are down here and are mentioned as procedural pain both for

placebo as well as sugammadex, nausea, vomiting, and anesthetic complication. An anesthetic complication is mentioned much more for sugammadex. This has to do with the fact that in Phase II studies the reversal agent was given during surgery so that some events like bucking, coughing or movement of a limb were reported as events, and I will come back to that later.

[Slide 134]

The incidence of adverse events as far as dose response is concerned if you look at the different doses that were investigated, the 2, 4 and 16 mg/kg dose, there does not seem to be a dose-response relationship.

[Slide 135]

There were no deaths related to the administration of sugammadex. In placebo-controlled trials a similar percentage of sugammadex subjects and placebo subjects experienced at least one SAE.

[Slide 136]

If we now look at serious adverse events in the pooled Phase I-III studies, five percent of all subjects exposed to any dose of sugammadex plus an NMBA experienced at least one SAE but then, again, looking at a potential

dose-response relationship there does not seem to be any.

[Slide 137]

There are a couple of specific adverse events I would like to discuss. Those are anesthetic complication, dysgeusia and hypersensitivity.

[Slide 138]

As I mentioned before, anesthetic complications include movement, for instance of a limb or the body, or coughing during the procedure or during surgery, grimacing, sucking on the endotracheal tube, or light anesthesia and these can be explained by the following:

[Slide 139]

In Phase II, mostly during the dose-finding trials, sugammadex was given during the procedure at a certain depth of blockade, and that could be 3, 5, 15, 1-2 PTC, or the reappearance of the second twitch, and this period was actually variable. So, if that happens, events like coughing, bucking movement, can actually occur and are being recorded as anesthetic complications.

In our Phase III trials, however, we have maintenance of neuromuscular blockade until the end of the procedure, and at the end of the procedure sugammadex is

given and then extubation takes place. So, a much lower frequency of these kind of events can be expected and was actually seen because if we looked at the incidences of anesthetic complications, we saw for sugammadex, in Phase II, an incidence of 5.9 percent, whereas if we look at Phase III the incidence for sugammadex was 0.7 percent and for neostigmine it was 0.5 percentB-quite comparable.

[Slide 140]

Dysgeusia or bitter taste-Bin our pooled Phase I trials we found in 12.6 percent of our sugammadex group versus 1.5 percent in the placebo group. One hundred percent was reported as related; 49 of the 56 cases occurred at doses of 32 mg/kg sugammadex or higher so at doses that we would not recommend for clinical use. They were short-lasting and self-limiting. In our pooled Phase II and Phase III trials there were only six cases reported, and only two of them were considered to be related.

[Slide 141]

Hypersensitivity-BI believe that the FDA also would like to discuss this and we, therefore, have prepared some more information on this issue as well. There was one subject who had a first exposure to sugammadex in a

volunteer study. The infusion stopped. This particular volunteer was supposed to have 32 mg/kg but it was stopped at approximately 8.4 mg/kg sugammadex due to paresthesia, visual disturbances, rash, stomach discomfort, palpitations, nausea, tachycardia and flushing. Now, this reaction was self-limiting. There was no treatment required and actually the investigator at first thought that this was a reaction of nervousness.

[Slide 142]

The subject, furthermore, had no known history of allergy. There was a slight increase in serum tryptase and that can be suggestive for a possible etiology of allergy. We did decide to do follow-up skin tests. Skin prick tests were performed. These were inconclusive. Also intradermal skin tests were performed and these were positive. So, overall the skin test conclusion was that this subject probably was hypersensitive to sugammadex. There was also some additional skin testing performed but there was no evidence for sensitization to other products that were tested.

[Slide 143]

We did feel that it was important to follow up

with this finding with a formal skin test study so we set up a skin test study. This was a single-center, placebo-controlled study investigating hypersensitivity with sugammadex through skin prick and intradermal tests.

The objectives there were to evaluate the skin prick tests and intradermal skin tests in healthy volunteers not previously exposed to sugammadex, but also to investigate the sugammadex hypersensitivity status of exposed, alleged hypersensitive volunteers of the 105, 106 and 109 trials.

[Slide 144]

The study consisted of two phases. The first phase was an open study in subjects not previously exposed to sugammadex and the second phase consisted of the first volunteer whom we previously identified as potentially hypersensitive, but also we scrutinized data from 156 subjects to find possible signs of allergy and put these subjects into the trial as well. Okay? There were six additional volunteers who were previously exposed to sugammadex, without any hypersensitivity symptoms, who were also put into the trial.

[Slide 145]

The results of this trial were that the potentially hypersensitive volunteer, the first one that we tested, the one that we found that we found with the intradermal test, tested positive again. Interestingly, this volunteer participated as a volunteer in many trials and it is unfortunate that we do not know his complete previous drug exposure.

Another conclusion was that no other allegedly hypersensitive subjects were hypersensitive to sugammadex based on the skin prick test and the intradermal test results.

One control subject had a positive intradermal test. This subject was previously exposed to sugammadex without previous clinical allergy symptoms, and also this subject had increased and comparable levels of urine methyl histamine both at baseline and post treatment, and this actually, according to our clinical expert, may indicate a false-positive outcome.

[Slide 146]

So, in overview and conclusion, we have one hypersensitive mild, self-limiting hypersensitive reaction in a healthy volunteer. There are no hypersensitivity

reactions reported in patients. In 182 subjects who received more than one dose of sugammadex there were no suspected hypersensitivity reactions reported. And, there are no reports of hypersensitivity associated with cyclodextrins in the literature.

[Slide 147]

Other safety data and risk management plan:

[Slide 148]

You may be interested in more detailed data on QTc. I am giving you only the top lines but we are willing to come back to this issue during the Q&A session. But we did do two thorough QTc trials which did not show QTc prolongation of concern. Furthermore, there were no clinically important laboratory changes in our studies as far as hematology, biochemistry and urinalysis is concerned.

[Slide 149]

We find it very important to implement a risk management plan and, therefore, we believe that it is important to study patients with severe renal failure for a prolonged period of time, and also the feasibility of hemodialysis, and we will do that separately.

But we will also implement activities including

active following on reports to obtain all relevant case information on potential adverse events; follow-up on off-label use; literature screening, and that is performed weekly on case reports; and periodic evaluation of reporting rates for selected AEs, for instance hypersensitivity. Of course, we are willing to work with the FDA to come to more structural approaches of risk management.

[Slide 150]

Our conclusion on safety is that the available clinical data that I have just shown you demonstrate that sugammadex is safe and well tolerated.

[Slide 151]

I would like to end this presentation and ask Dr. Ronald Miller to summarize our presentation for today.

Summary

DR. MILLER: Thank you very much. As indicated in my previous presentation, I have had a long, 30-40-year history of successfully performing research in the development of neuromuscular blocking drugs. As I said before, I and we tried very hard to develop an outstanding reversal drug and even failed to develop a mediocre reversal drug. Our failure then dictated a different approach to the

development of a new reversal drug which is exactly what you have heard today.

[Slide 152]

So, I would like to review the definition of an unmet medical need, as at least I define it, and review where we are now. I believe that sugammadex will minimize or eliminate the need of neostigmine.

I believe it will minimize or eliminate the need for succinylcholine, and it will attenuate the incidence of postoperative paralysis. It will increase the intraoperative flexibility by providing a variable depth of neuromuscular block with confidence that you, as anesthesiology deliverers, can reverse the block successful, and I believe that ultimately there will be an increase in perioperative patient safety.

As an anesthesiologist, I would like to expand and just briefly refresh your memory with regard to the first two points, that is to say, neostigmine and succinylcholine.

[Slide 153]

So, let=s first deal with neostigmine. You actually have already seen these data. The data have been converted into this block diagram to better emphasize the

difference in magnitude between sugammadex and neostigmine.

So just to review, this is time in minutes after administration of sugammadex versus neostigmine and this is rocuronium and vecuronium. I think you can clearly see that the time for recovery of the Train-of-Four ratio of 0.9 is 2.7 minutes versus 49 minutes; 3.3 minutes versus 49 minutes. So, clearly the quickness of reversal with sugammadex is dramatically, dramatically more rapid in reversing a profound block than is neostigmine.

[Slide 154]

Another issue with t neostigmine is on this slide in that it compares heart rate with sugammadex and the neostigmine/glycopyrrolate combination. Despite the clinician=s efforts for matching glycopyrrolate and neostigmine appropriately, it is frequent that we have a transient tachycardia.

So, if we examine this particular slide you can see on the vertical axis the percent increase in heart rate, and this is time in minutes. These arrows represent the time at which either sugammadex or neostigmine was given. This arrow means that the patient has had his or her trachea extubated and most likely the patient is in the recovery

room.

I think you can see by looking at this that the orange line indicates that there is no change in heart rate with sugammadex. In contrast, the very predictable reported on multiple occasions transient increase in heart rate occurs with the neostigmine/glycopyrrolate combination.

The goal in anesthesia one might say, especially geriatric anesthesia, is to minimize changes in heart rate which we are frequently unable to do with the neostigmine/glycopyrrolate combination. So, this is another clear difference between the neostigmine/glycopyrrolate combination and sugammadex.

[Slide 155]

Now I am going to switch to succinylcholine. This is obviously an important slide and you have seen it before. I would like everyone to recognize the importance of this slide in a very specific way, and that is to focus on succinylcholine itself. As you know, this compares rocuronium/sugammadex and succinylcholine. Succinylcholine has a very rapid onset and a very rapid offset in neuromuscular blockade. Can we replace succinylcholine with a combination of rocuronium and sugammadex?

This slide, as you know, compares 10 and 90 percent recovery of T_1 and, as you can see, the recovery or the offset time of the sugammadex/rocuronium combination is actually quicker in both areas than is succinylcholine.

Even amazingly, if you compare 90 percent recovery of T_1 of the sugammadex drug with succinylcholine at a time when recovery is well on its way to complete with sugammadex, succinylcholine is just now thinking about recovery, if I can put human terms on it, or is right around at 10 percent. So, when the question arises can rocuronium and sugammadex replace succinylcholineB-and don=t forget all of its associated side effects, the answer to this question has to be yes.

[Slide 156]

So, sugammadex is one of the most innovative drugs in anesthesia for many years. A few years ago I was told that there was a drug that could actually pick up rocuronium, if I can use lay person termsB-pick up rocuronium, take it away from the neuromuscular junction and deposit it some place else.

When I was told that I said, okay, tell me another story and I don=t mean to dramatize in such a serious forum

as this but that is actually the way I thought about it. I thought it can=t possibly be true after all those years I spent failing.

But this is the first drug that encapsulates the neuromuscular-blocking drug, taking it away from the neuromuscular junction and terminating its action. It also allows increased flexibility with neuromuscular-blocking drugs intraoperatively, which I mentioned before, that is to say that we will be able to provide the depth of block really clinically necessary knowing that we have a much more reliable antagonist.

[Slide 157]

So in summary, it provides a complete and rapid reversal of profound neuromuscular blockade; minimizes the risk of residual postoperative paralysis; elimination of managing side effects associated with drugs like neostigmine when combined with muscarinic antagonists, such as glycopyrrolate or atropine; and the mechanical mixing of the two drugs.

You might think that I am preoccupied with this mixing of two drugs issue but we need, as anesthesiologists or physicians overall, to take every opportunity possible to

prevent potential error and I think this is a modest step in the right direction. Lastly, in combination with rocuronium, it may provide an alternative to succinylcholine.

[Slide 158]

So, sugammadex has been shown to be safe and efficacious in more than 2,000 administrations in patients and volunteers. I believe that its properties are and will lead to safety benefits for patients. And, sugammadex will become a valuable new drug in the management of neuromuscular blockade specifically and general anesthesia overall.

This represents the completion of our formal presentation. Thank you very much.

DR. FARRAR: Thank you very much for the presenters. What we would like to do now is to open a brief period for the members of the committee to ask questions about the presentation. Just to remind the committee members, this is not a time for formal discussion but really for clarification of some of the material that has been presented. Please feel free to ask questions. Dr. Nichols?

Questions from the Committee

DR. NICHOLS: This is a two-part question for Dr. Dobbelsteen on his toxicology model. I wondered if the model that was presented has been used in other drugs that are currently available today on the market, particularly in children, and if there has ever been an instance in which the toxicology effects, particularly on bone and teeth, have been underestimated by that model.

DR. BOEN: Dr. van Den Dobbelsteen?

DR. VAN DEN DOBBELSTEEN: Thank you. Could you please identify yourself, where the question is coming from?

DR. NICHOLS: Yes. I am David Nichols, from Johns Hopkins.

DR. VAN DEN DOBBELSTEEN: Could you be more specific on which model you are indicating. Specifically the juvenile rat model?

DR. NICHOLS: Yes, correct, the juvenile rat model.

DR. VAN DEN DOBBELSTEEN: We know from the young adult rat model that it has been used a lot. The juvenile rat model has been introduced into toxicology, like, in the last five years or so. So, I think there won=t be very much reference data. But the much more appropriate person to answer this question, who has been a long time in this

field, would be Prof. Harry Genant. I hope he can address your question.

DR. GENANT: Good morning. My name is Harry Genant. I am a professor emeritus at UCSF and also a co-founder of Synarc and a member of the board of directors, a company that participates in clinical trials, particularly in the field of osteoporosis.

Now, with regard to the question of the adequacy of the rat model, particularly the young rat model or the juvenile rat model, and whether there has been in its very broad use in the context certainly of bone-active drugs--whether there has been experience with underestimation of the potential toxicity, I am not aware of any experience that would indicate that this has been the case.

Indeed, the rat model is the most widely used preclinical model for all of the drugs that have been approved for treatment of osteoporosis. So, typically one has been able to extrapolate very readily from the experience in the rat, including the juvenile rat, to the human experience. Thank you.

DR. FARRAR: Did you want to clarify something for the committee, Dr. Rosebraugh?

DR. ROSEBRAUGH: I would like to clarify something for the committee. On slides 142 through 145 and part of 146 this is all new data that the sponsor has just submitted to us recently so we haven=t had a chance to review it yet.

DR. FARRAR: Dr. Soriano?

DR. SORIANO: Yes, this is a follow-up question on toxicity to the bone. Certainly this is a striking finding that you have reported. Again, this is a question regarding the model itself. How long did the model last? What was the endpoint there? Were these things tested in adulthood in the rat?

And, there are two things I want to ask about the testing itself. Was there any functional testing, such as load bearing on these rat bones? The second question is was there any incidence of tumorigenesis with this effect?

DR. BOEN: Dr. van Den Dobbelsteen, would you be able to address that?

DR. VAN DEN DOBBELSTEEN: In your question there are a couple of ones. Please tell me if I am not complete in my answer. First of all tumorigenesis, your last question, typically compounds dosed for single dose units are not assessed for carcinogenicity. Only if you would

have prolonged exposure and prolonged dosing over six months you would do that. Typically the class of cyclodextrins has not been associated with carcinogenicity at all. There have been various studies, both using the oral and intravenous routes and dosing over two years, and there has been no report of carcinogenesis in the rat and mouse model, I believe.

Regarding our models more technically, we have used adult rats and juvenile rats in a single-dose regimen and four weeks of dosing and that also included groups that went for recovery periods. The functional assessment of what was happening on bone has been assessed in two studies, single-dose studies and data that I showed you on 500 mg/kg. The rat was dosed a single dose and at weekly intervals after that dose we would sacrifice animals and would do micro-CT assessments on them.

In another study we have also done bone strength measurements. So, we have taken the femur and assessed basically three endpoints. One endpoint was trabecular bone strength. So, there you have a cone of trabecular bone and introduce a lot of force to it and see how it responds.

Can I call a backup slide actually? It may

enlighten it a bit. It is N-110. Slide on, please.

[Slide N-110]

Thank you. Here you see the kind of parameters that you can assess by microcomputer tomography. I am not really the appropriate person to speak on this because Prof. Harry Genant has over 30 years experience on this technology. But what you can do is at a very detailed level assess the microanatomical structure of bone and this is basically what we have been doing both for the young adult rat model as well as the juvenile rats.

[Slide N-111]

In addition to that, in the young adult rat model we have been applying bone strength measurements. That basically assesses the three-point bending, the trabecular indentation test so assessing trabecular strength, and femur neck cantilever tests. These are representative endpoints for overall bone strength regarding the femur. The different kind of parameters that you can measure are listed below. I think the next slide would also be appropriate. Slide on, please.

[Slide N-112]

These are the biochemical markers for bone

turnover that we have assessed other in plasma or in urine, and this is regarded to be an appropriate test for estimating an effect on bone turnover. But, as indicated in all of my presentation, we have not seen any effects on parameters like this up to the dose of 500 mg/kg which represented a safety margin of 70 to 1,000.

DR. FARRAR: Ms. Aronson, do you have a follow up?

MS. ARONSON: Yes, thank you. Following up on that discussion, I am wondering about the study with the adult population and how much of that adult population was geriatric. I am thinking in relationship to emergency surgery for hip fractures and the presentation about the product staying in the system a bit longer for the elderlyB- yes, I think it was the elderly population.

DR. BOEN: We are very lucky that we have Dr. Terri Monk here, who participated in the study as an investigator.

DR. MONK: Yes, I was the principal investigator at Duke in the geriatric trial. Do we have the slides that show the study design? Basically, as they are looking for those slides, this study included 140 patients. They had 40 patients who were between the ages of 18 and 65. Slide up.

[Slide E-99]

If you look, 18 to 64 years was the adult group and they were the younger comparator group. We had 40 patients in that group. In the 65 to 74 year group we had 60 patients and in the greater than or equal to 75 year group we had 40 patients. So, that would be a total of 100 geriatric patients who were in that trial. We used a typical intubating dose of rocuronium, 0.6 mg, and then at the occurrence of the second twitch, T_2, after the last dose we gave sugammadex in a dose of 2 mg/kg. Let=s see the next slide.

[Slide E-100]

If you look at the amount of time to reversal, really even though it was slightly prolonged in the elderly person, we are talking in terms of one minute longer. It was about 20 seconds longer in the middle age group, 65 to 74, for onset to a full reversal of a Train-of-Four ratio of 90 percent. In the over 75 year old group it was one minute longer. So, even though it was maybe slightly longer, it is really not clinically significant at all. So, it was very efficacious in this.

You were also asking about hip fracture patients. We did include orthopedic patients in that trial. We

didn=t do any specific bone analysis but if you go back to the toxicology and you look at the elderly adult you can see there is very little distribution in the bone in the elderly adult. It is much, much lower than in the young juvenile.

Also, the elimination is not really increased in the elderly patient. The elimination half-life is very similar, in the range of 2 to 2.5 hours for one half-life.

MS. ARONSON: That would be the same for geriatric patients with osteoporosis?

DR. MONK: Yes.

DR. FARRAR: Dr. Eisenach?

DR. EISENACH: I had a question about drug-drug interactions, and that relates to lipophilic drugs of abuse. I suspect you have studied the opioids extensively. I don=t know if you have looked at heroin. Have you looked at THC? Have you looked at the stimulants? My thought is, is this a drug that could be used to hide drugs of abuse?

A second part of that, of course, is steroid doping in athletes. Is this a drug that could be given intramuscularly to remove rapidly steroids from the system in drug testing? I mean, it is an issue that I think you may have already considered but one that you should consider

if you haven=t in your preclinical studies.

DR. BOEN: Right, I think that is a good question. I would like to ask Dr. Ton Bom to address that question.

DR. BOM: Well, we have only looked, of course, at clinical use opioids because you saw my criteria. The drugs you were just mentioning there are recreational drugs and, of course, not drugs that are commonly used in anesthesia, I hope. But maybe we can show some slides about some opioids, if we can find them.

DR. EISENACH: The question of steroids I think is important because of the androgens that are used in sport settings and the huge publicity and the drug testing that occurs with them. So, I don=t know anything about whether this drug is active when given intramuscularly, whether it is absorbed and would be effective in that setting but I think it is something that should be addressed at the preclinical time.

DR. BON: We have looked at, for instance, testosterone which has no affinity at all for sugammadex. It is a commonly misused drug by body builders and people like that. I can also show you some slides about the opioids. Slide up, please.

[Slide N-41]

You see some analgesics just in general. You see there is no affinity for fentanyl, no affinity to alfentanil, nor for certaminophen; very low affinity for morphine, hydrocodone and codeine. Next slide, please.

[Slide]

We also looked at nalmefane, oxycodone, pethidine, fenoxypyridine, propoxyphene and remifentanil, and only remifentanil is the one that we found, as I already told you, that was the one with the highest affinity but when you compare to rocuronium it is still very, very low. I hope that addresses your question.

DR. BOEN: And other drugs that fall within this category would probably be very applicable for further investigation in a postmarketing surveillance situation.

DR. FARRAR: Any other questions?

DR. NUSSMEIER: This is a question for Dr. Miller or anyone who may care to answer. If the drug is approved, my understanding is that at least at present its use would be discouraged or even contraindicated in patients with end-stage renal disease, on dialysis.

DR. BOEN: That is correct. We currently

discourage use in patients with severe renal failure. That is not based on adverse findings in our clinical study but we only did 15 patients and we did find that the clearance was 17-fold decreased. So, we do feel that we need to do a further, extended safety study before we can actually recommend the use in these kind of patients.

DR. NUSSMEIER: The alternatives would need to remain available for that population. Part two of that question is renal insufficiency, and what would be the minimum creatinine clearance that would be acceptable.

DR. BOEN: Well, currently, based on our study, we maintain a level of 30 ml/minute.

DR. NUSSMEIER: Thinking as a clinician, I am just wondering how that would translate in the recommendations regarding the need to calculate the creatinine clearance to make a decision in an individual patient.

DR. BOEN: We would define patients with severe renal dysfunction as patients with a creatinine clearance of less than 30 ml/minute. Dr. Monk, would you like to comment?

DR. MONK: I can make a comment. I was involved in the geriatric study and, as you know, even normal

creatinines in a geriatric patient probably indicate an upper normal renal insufficiency.

We were allowed in that study to go to creatinines of 2, which in a geriatric patient is quite impaired and probably would be similar to what he is saying about 30 ml/minute, and we had absolutely no problem with prolongation or any problems in these patients. So, clinically I think that you are going to be able in very elderly patients to go to creatinines of at least 2.0, 2.5 without any difficulty.

DR. FARRAR: Just one very quick one, could I just follow up for one second? Is the drug dialyzable?

DR. BOEN: There were in vitro experiments where the drug was dialyzable with high flux dialysis. In our renal study we performed high flux dialysis in four patients. For two we got consistent results; for two others we could not and that is the reason why we would do a repeat study in that population.

DR. FARRAR: Dr. Deshpande?

DR. DESHPANDE: A couple of questions. One, you mentioned the use of sugammadex in emergency situations and, therefore, reversal in that regard. Often these patients

need to come back or within the same operating room experience need to be again blocked and, therefore, cared for. What about after the first use of sugammadex the use of neuromuscular blockade and what are the choices we have there?

DR. BOEN: There are several options available. One of the best options if there is a real need for speed to do another intubation with a neuromuscular blocking agent would be to use a benzoquinoline drug or a succinylcholine because sugammadex does not bind to these compounds. Another option would be to use a waiting time, and we actually propose to apply a table within the package insert showing what kinds of waiting times you can expect. The third option would be to use an LMA or to do an intubation with higher doses of propophyl without an NMBA.

DR. DESHPANDE: My point is that use of a similar blocking agent is really not possible for several hours after. Do you know what that time frame is?

DR. BOEN: Slide on.

[Slide P-23]

Here you see the table that I was referring to. For instance, if the administered dose of sugammadex was 2