

Report on the Deliberation Results

October 27, 2009

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Bridion Intravenous 200 mg Bridion Intravenous 500 mg
[Non-proprietary name]	Sugammadex Sodium (JAN*)
[Applicant]	Nippon Organon K.K. (a predecessor of Schering-Plough K.K.)
[Date of application]	December 20, 2007

[Results of deliberation]

In the meeting held on October 21, 2009, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

**Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Report

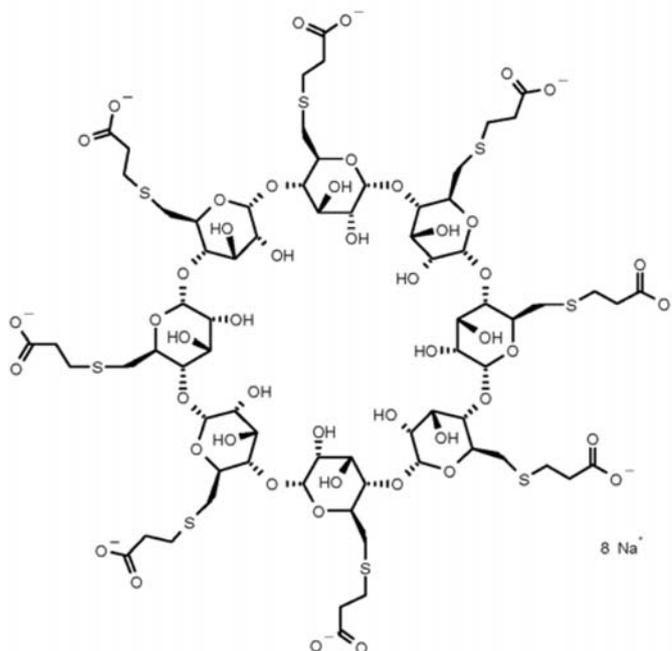
October 2, 2009

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Bridion Intravenous 200 mg Bridion Intravenous 500 mg
[Non-proprietary name]	Sugammadex Sodium
[Name of applicant]	Schering-Plough K.K. (Nippon Organon K.K. at the time of submission)
[Date of application]	December 20, 2007
[Dosage form/Strength]	A solution for injection containing sugammadex sodium equivalent to 200 mg or 500 mg sugammadex per vial
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: C₇₂H₁₀₄O₄₈S₈Na₈

Molecular mass: 2178.01

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Chemical name:

Cyclooctakis-(1→4)-{6-S-[2-(sodium carboxylato)ethyl]-6-thio- α -D-glucopyranosyl}

[Items warranting special mention] None

[Reviewing office] Office of New Drug III

Review Results

October 2, 2009

[Brand name]	Bridion Intravenous 200 mg Bridion Intravenous 500 mg
[Non-proprietary name]	Sugammadex Sodium
[Name of applicant]	Schering-Plough K.K. (Nippon Organon K.K. at the time of submission)
[Date of application]	December 20, 2007

[Results of review]

Based on the submitted data, it is determined that the efficacy and safety of the proposed product in the reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide have been demonstrated.

However, the efficacy and safety of the proposed product have been evaluated using foreign clinical data, based on the results from 2 bridging studies for routine reversal of shallow (at the reappearance of T₂ [the second twitch in response to train-of-four (TOF) stimulation], as detected with a neuromuscular monitor) and profound (at 1-2 PTCs [1-2 post-tetanic counts] [1-2 responses to post-tetanic twitch stimulation], as detected with a neuromuscular monitor) neuromuscular blockade and there are limited clinical data at the recommended clinical doses in Japanese patients. Therefore, a drug use-results survey should be conducted promptly to fully investigate the safety of the product especially regarding hypersensitivity or allergic reactions, bleeding-related adverse events, and re-occurrence of blockade or residual blockade in a broad range of Japanese patients, including patients with impaired renal or hepatic function, geriatric patients, children, and pregnant women/nursing mothers. It is also necessary to investigate the influences of the neuromuscular blocking agent used (rocuronium bromide or vecuronium bromide), the level of neuromuscular blockade to be reversed by the proposed product, and the use of a neuromuscular monitor on the efficacy and safety of the proposed product, and the details of administration and the safety of the proposed product when it had to be re-administered or a neuromuscular blocking agent was re-administered after sugammadex administration. Since there are no Japanese clinical data regarding immediate reversal of neuromuscular blockade following an intubating dose of rocuronium bromide, a special drug use-results survey should be conducted to collect much information as early as possible and the obtained information should be provided to medical practice.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the proposed product may be approved for the following indication and dosage and administration.

[Indication]

Reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide

[Dosage and administration]

The usual adult dose is 2 mg/kg as sugammadex administered intravenously for routine reversal of shallow neuromuscular blockade (if the reappearance of the second twitch [T_2] in response to train-of-four [TOF] stimulation has been detected with a neuromuscular monitor) and 4 mg/kg as sugammadex administered intravenously for routine reversal of profound neuromuscular blockade (if 1-2 responses to post-tetanic twitch stimulation [1-2 post-tetanic counts (1-2 PTCs)] have been detected with a neuromuscular monitor). If there is a clinical need for immediate reversal following an intubating dose of rocuronium bromide, the usual adult dose is 16 mg/kg as sugammadex administered intravenously at about 3 minutes after the administration of rocuronium bromide.

Review Report (1)

August 10, 2009

I. Product Submitted for Registration

- [Proposed brand name] Bridion Intravenous 200 mg/2 mL
 Bridion Intravenous 500 mg/5 mL
- [Non-proprietary name] Sugammadex Sodium
- [Name of applicant] Schering-Plough K.K. (Nippon Organon K.K. at the time of submission)
- [Date of application] December 20, 2007
- [Dosage form/Strength] A solution for injection containing sugammadex sodium equivalent to 200 mg or 500 mg sugammadex per vial
- [Proposed indication] Reversal of the neuromuscular blocking effect of rocuronium bromide or vecuronium bromide
- [Proposed dosage and administration]

The usual adult dosage for intravenous administration is as shown below.

	Dose (as sugammadex)
Routine reversal of neuromuscular blockade (shallow blockade)	2 mg/kg
Routine reversal of neuromuscular blockade (profound blockade)	4 mg/kg
Immediate reversal (3 minutes after an intubating dose of rocuronium bromide)	16 mg/kg

II. Summary of the Submitted Data and the Outline of Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Sugammadex Sodium (sugammadex), the active ingredient of the product, is a γ -cyclodextrin derivative, which was synthesized as a reversal agent for a non-depolarizing neuromuscular blocking agent, rocuronium bromide (rocuronium), through molecular design by Organon (a predecessor of Schering-Plough) and it forms inclusion complexes with the neuromuscular blocking agents that contain a steroid skeleton (steroidal neuromuscular blocking agents),

rocuronium and vecuronium bromide (vecuronium), preventing their action and reversing neuromuscular blockade.

Overseas, a clinical trial of sugammadex was initiated in [REDACTED] 20[REDACTED] and its EU marketing authorization was granted in July 2008. As of June 2009, sugammadex has been approved in 33 countries including Australia and New Zealand. In Japan, bridging studies based on the bridging concept were conducted since a phase I trial carried out in [REDACTED] 20[REDACTED] in the UK suggested pharmacokinetic similarities between Japanese and Caucasian subjects.

Since it has been determined that foreign clinical data can be extrapolated for the evaluation of the efficacy and safety of sugammadex and its efficacy and safety in the reversal of rocuronium- or vecuronium-induced neuromuscular blockade have been confirmed, the applicant has now filed a marketing application.

In Japan, an acetylcholinesterase inhibitor, neostigmine (Vagostigmin Injection etc.) and its combination product (AtvagoReverse Intravenous Injection Syringe) indicated for reversal of the effects of non-depolarizing neuromuscular blocking agents, have been approved.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

The drug substance Sugammadex Sodium is a modified γ -cyclodextrin (cyclic octamer of glucose) with every sixth carbon hydroxyl group substituted with a thioether linked to a propionate group (eight side chains added). It is a white powder or granules and its general properties including description, solubility, hygroscopicity, melting point, pH, dissociation constant (pKa), optical rotation, and crystalline polymorphism have been determined. It is hygroscopic and exists in different crystalline forms, including an amorphous form. It has 40 asymmetric carbons (5 asymmetric carbons in each glucose unit) and its configuration is preserved by [REDACTED] [REDACTED] of [REDACTED].

The manufacturing process for the drug substance consists of Step 1 ([REDACTED] [REDACTED]), Step 2 ([REDACTED]), Step 3a ([REDACTED]), Step 3b ([REDACTED]), and Step 4 (packaging and labeling) and a reprocessing step has been included after each of Step [REDACTED] and Step [REDACTED]. Step [REDACTED] and Step [REDACTED] have been defined as critical steps and control items and control values have been established for an intermediate [REDACTED].

The chemical structure of the drug substance has been elucidated by single-crystal X-ray diffraction, elementary analysis, mass spectrometry, ultraviolet spectrophotometry (UV), infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (¹H-NMR, ¹³C-NMR), and inductively coupled plasma-atomic emission spectrometry (ICP-AES). The general properties and chemical structure of [REDACTED] [REDACTED] Org48302 have been determined in the same manner as those of the drug substance. As other impurities, related substances, residual solvents, and inorganic impurities have been analyzed.

The proposed specifications for the drug substance include description, identification (IR, liquid chromatography [HPLC], sodium [ICP-AES]), purity (heavy metals and [REDACTED] [ICP-AES], related substances [HPLC], residual solvents [REDACTED] and [REDACTED] [gas chromatography (GC)]), water content, bacterial endotoxins, microbial limits, sodium content (ICP-AES), and assay (Sugammadex Sodium, Org48302, Sugammadex Sodium + Org48302 [HPLC]). In the course of regulatory review, a specification for [REDACTED] (Sugammadex Sodium + Org48302 + [REDACTED]) has been newly established and the specification limits for assay (Sugammadex Sodium, Org48302, Sugammadex Sodium + Org48302) have been changed based on the results of batch analyses. For related substances,¹⁾ specifications for 14 different related substances (Related Substance A, Org48301, Related Substance B, Related Substance D, Related Substance E, Related Substance F, Related Substance G, Related Substance H, Related Substance I, Related Substance J, Related Substance K, Related Substance L, Related Substance M, Related Substance N), other individual related substances, and total related substances have been set. In the course of regulatory review, the specifications limits for 4 different related substances (Related Substance A, Related Substance D, Related Substance F, Related Substance G) have been changed based on the results of batch analyses. [REDACTED] may arise in the manufacturing process of the drug substance and at regulatory submission, a different specification limit ([REDACTED]%) from other individual related substances was proposed for control of other unidentified [REDACTED] based on the safety of [REDACTED] reported in published literature etc., which has been changed in the course of regulatory review so that they are controlled as part of other individual related substances (specification limit, [REDACTED]%).

For stability evaluation of the drug substance, long-term testing (25°C/60%RH/dark place, 24 months), intermediate testing (30°C/65%RH/dark place, 12 months), and accelerated testing

¹⁾ Of the 14 specified related substances, potential coelution of two compounds was indicated for [REDACTED] 3 related substances, which have been identified as [REDACTED] [REDACTED] (Related Substance K-1, Related Substance K-2), [REDACTED] [REDACTED] (Related Substance L-1, Related Substance L-2), and [REDACTED] [REDACTED] (Related Substance M-1, Related Substance M-2), respectively. With respect to [REDACTED] [REDACTED], Related Substance K-1 has so far been detected in the drug substance while Related Substance K-2 has been detected as a degradation product in the drug product.

(40°C/75%RH/dark place, 6 months) were performed using 3 pilot scale batches²⁾ of the drug substance packaged in double polyethylene bags/polyethylene containers and stress testing (light [an overall illumination of not less than 1.2 million lx·hr and an integrated near ultraviolet energy of not less than 200 W·h/m², double polyethylene bags/with or without aluminum foil]) was performed using 1 pilot scale batch of the drug substance. The attributes tested in these studies include description, identification (██████████), purity (related substances [HPLC], residual solvents [██████████]), water content, bacterial endotoxins, microbial limits (tests for bacterial endotoxins and microbial limits were not performed in the stress testing), and assay (Sugammadex Sodium, Org48302, Sugammadex Sodium + Org48302 [HPLC]). In addition, tests for ██████████, ██████████, and ██████████ were performed in the long-term testings and test for ██████████ was performed in the intermediate and accelerated testing. Using 4 commercial scale batches of the drug substance packaged in double polyethylene bags/with or without an aluminum-laminated bag (only 3 batches packaged without an aluminum-laminated bag)/polyethylene containers, long-term testing (25°C/60%RH/dark place,³⁾ 24 months), intermediate testing (30°C/65%RH/dark place, 24 months⁴⁾), and accelerated testing (40°C/75%RH/dark place, 6 months) were performed. The attributes tested in these studies include description, purity (related substances [HPLC], residual solvents [GC]), water content, bacterial endotoxins, microbial limits (tests for bacterial endotoxins and microbial limits were not performed in the accelerated testing), and assay (Sugammadex Sodium, Org48302, Sugammadex Sodium + Org48302 [HPLC]). In all studies, there were a decrease in assay of Sugammadex Sodium over time, increases in Related Substance E and Related Substance I, and a decrease in Related Substance D⁵⁾ and assay result of Sugammadex Sodium fell below the specification limit for 1 commercial scale batch,⁶⁾ but all others were within the specification ranges.⁷⁾ When packaged without an aluminum-laminated bag, there was an increase in water content over time exceeding the specification limit, but no effects on assay or related substances were observed and no significant change in the quality occurred for other attributes tested. Based on the results of these studies, a storage condition of “store in tight containers at ██████████°C to ██████████°C, protected from light” and a re-test period of ██████████ months have been proposed for the drug

²⁾ Although changes were made to the manufacturing process (██████████ ██████████ and ██████████ ██████████ in Step ██████████) after the 3 drug substance batches used in the stability studies were produced, the applicant discussed that these changes do not affect ██████████ other than Org48302 (██████████ ██████████ ██████████ ██████████) (██████████ compound) and Org48301 (██████████ ██████████ ██████████ ██████████).

³⁾ Long-term testing was also performed under the condition of ██████████°C/ambient humidity/dark place.

⁴⁾ Data up to 12 months were presented for 1 of the 4 batches packaged with an aluminum-laminated bag.

⁵⁾ The applicant discussed that a decrease in Related Substance D was due to ██████████ ██████████ ██████████ ██████████.

⁶⁾ One commercial scale batch of the drug substance failed to meet the specification for assay of Sugammadex Sodium (up to ██████████%), which has been discussed to be due to assay result of ██████████ exceeding the specification limit in this batch (██████████ had not been included in the drug substance specification at the time of producing this batch).

⁷⁾ The specification limits for assay (Sugammadex Sodium, Org48302, Sugammadex Sodium + Org48302) have been changed in the course of regulatory review. Two of the 3 pilot scale batches used in the stability studies of the drug substance failed to meet the new specification for assay at the start of the studies, but no significant change (failure to meet the old specification) occurred during the study period.

[HPLC]). In the course of regulatory review, the specification limits for assay (sugammadex, the free acid of Org48302, sugammadex + the free acid of Org 48302) have been changed due to a change to the drug substance specification for assay of Related Substance Org48302. For related substances (degradation products), specifications for Related Substance E, Related Substance I, Related Substance C, Related Substance G, Related Substance D, Related Substance K, other individual degradation products, and total degradation products have been established. In the course of regulatory review, a specification for Impurity A which arises in [REDACTED] step has been newly set and the specification limits for individual degradation products have been changed based on the results of batch analyses and stability studies.

For stability evaluation of the drug product, long-term testing (25°C/60%RH/dark place,⁹⁾ upright¹⁰⁾ or inverted position, 36 months) and accelerated testing (40°C/75%RH/dark place, inverted position, 6 months) were performed using 3 pilot scale batches each of the 200 and 500 mg strengths packaged in glass vials/rubber stoppers/aluminium caps and stress testing (light [an overall illumination of not less than 1.2 million lx·hr and an integrated near ultraviolet energy of not less than 200 W·h/m², glass vials/rubber stoppers/aluminium caps, light exposure, packaged in carton or black polyethylene foil, horizontal position]) was performed using 2 pilot scale batches each of the 200 and 500 mg strengths. The attributes tested in these studies include description, identification, osmolality, pH, purity (related substances), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, and assay and container/closure integrity testing was also performed. Under the long-term and accelerated conditions, a decrease in assay of sugammadex over time, increases in Related Substance E, Related Substance I, Related Substance C, Related Substance G, and Related Substance K, and a decrease in Related Substance D were observed, which were all within the specification ranges. Under the stress condition (light exposure), in addition to these changes, there were a decrease in Org48302 and increases in other related substances and the samples failed to meet the acceptance criteria for Related Substance K, other individual degradation products, and total degradation products (up to [REDACTED]%, [REDACTED]%, and [REDACTED]%, respectively). Under the accelerated condition, color changed (the light yellow-brown color darkened), which was within the specification. There were no changes over time for other attributes tested. Based on the results of these studies, a storage condition of “store protected from light at room temperature” and a shelf life of 3 years have been proposed for the drug product.

⁹⁾ Long-term testing was also performed under the conditions of [REDACTED]°C/ambient humidity/dark place, [REDACTED]°C/[REDACTED]%RH/dark place, and 30°C/75%RH/dark place.

¹⁰⁾ Samples stored in the upright position were tested only for bacterial endotoxins, sterility, and container/closure integrity at 12, 24, and 36 months.

2.B.(3) Stability studies of the drug substance

In the stability studies using commercial scale batches of the drug substance, an aluminum-laminated bag was used in addition to the marketing pack. An aluminum-laminated bag was good for humidity protection and when packaged without an aluminum-laminated bag, there was an increase in water content over time, which failed to meet the specification. Therefore, PMDA asked the applicant to explain the stability of the drug substance in the marketing pack (without an aluminum-laminated bag) during the re-test period.

The applicant explained as follows:

In order to reduce the amount of the drug substance to be used for stability studies using commercial scale batches of the drug substance, small packs of the drug substance for different time points (the amount sufficient to perform each test ■ times) were stored individually, which was a more severe condition in terms of the drug substance surface area/headspace ratio in the container, compared with the drug substance in the marketing pack and the drug substance is hygroscopic. Thus, it was predicted that the stability behavior of water content of the drug substance in small packs would not represent that of the drug substance in the marketing pack, resulting in failure to meet the specification. Then, the effect of an aluminum-laminated bag was investigated using small packs of the drug substance stored under the same condition. As a result, when packaged without an aluminum-laminated bag, an increase in water content and a decrease in ethanol were observed, but there were no effects on other attributes tested, e.g. assay and related substances. In the stability studies using 3 pilot scale batches of the drug substance, the drug substance surface area/headspace ratio was the same as that in the marketing pack and the effects of water and oxygen were also investigated, but no significant change occurred. The results of retesting of 2 batches of bulk drug substance in the marketing pack conducted overseas to date have shown that the drug substance is stable for at least ■ months. Therefore, the drug substance is considered stable during the re-test period when stored in the proposed marketing pack under the recommended condition.

2.B.(4) Change of the color of the drug product

PMDA asked the applicant to explain in details about an investigation of change of the color of the drug product.

The applicant explained as follows:

The cause for change of the color of the drug product (the light yellow-brown color darkened) was investigated using liquid chromatography-ultraviolet-visible spectrophotometry (LC-UV/VIS) and liquid chromatography-mass spectrometry (LC-MS), which suggested that

trace amounts of varieties of unspecified degradation products (unidentified), instead of a single degradation product, were involved and in addition to [REDACTED] [REDACTED] investigated in formulation development, [REDACTED] and [REDACTED] content of the drug substance, [REDACTED], [REDACTED] [REDACTED], and [REDACTED] during the manufacture of the drug product, and [REDACTED] were considered to affect the color of the drug product. Therefore, [REDACTED] and [REDACTED] have been included in the drug substance specification and the relevant manufacturing process steps have been improved.

One of the drug product batches used in the stability studies of the drug product was produced using the drug substance batch ([REDACTED] content, [REDACTED] ppm) that failed to meet the acceptance criteria for [REDACTED] (\leq [REDACTED] ppm). PMDA asked the applicant to explain the appropriateness of establishing the storage condition and shelf life for the drug product based on the results of stability studies using this batch.

The applicant explained as follows:

At the time of producing the drug product using this drug substance batch, [REDACTED] was not included in the drug substance specification, but the deviation from the specification limit established later was slight and the results of stability studies on this drug product batch produced using this drug substance batch were similar to those on other batches, including the total level of degradation products, and color also did not change. Therefore, the proposed storage condition and shelf life for the drug product are considered appropriate.

Based on the above review, PMDA concluded that there are no particular problems with the proposed specifications, test procedures, storage condition, and shelf life for the drug substance and the drug product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

The effective concentration (EC₉₀) or dose¹¹⁾ (ED₉₀) of a neuromuscular blocking agent producing 90% block was calculated in each study for guinea pigs and in preliminary studies for other animal species. Doses of sugammadex are expressed as the free acid in safety pharmacology studies and as the sodium salt in other studies and various neuromuscular blocking agents and sugammadex (including the active metabolite of vecuronium and related substances of sugammadex) were all administered intravenously in *in vivo* studies. Unless otherwise specified, the data are expressed as the mean or the mean \pm standard error (SE).

¹¹⁾ The clinical doses of neuromuscular blocking agents are 2 to 3 times the ED₉₀.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1 Studies on primary pharmacodynamics of sugammadex (4.2.1.1.1)

(a) Isothermal microcalorimetry

The association constant (K_a value) of sugammadex with various neuromuscular blocking agents, as determined by isothermal microcalorimetry, was 161.5 ± 28.1 , 15.1 ± 1.9 , 8.8 ± 0.4 , 6.0 ± 0.2 , and $2.6 \pm 0.2 \times 10^6 \text{ M}^{-1}$ for steroidal neuromuscular blocking agents, pipecuronium (unapproved in Japan), rocuronium, vecuronium, 3-OH-vecuronium (the active metabolite of vecuronium), and pancuronium, respectively. Meanwhile, sugammadex showed little affinity for non-steroidal neuromuscular blocking agents, *d*-tubocurarine, suxamethonium, etc. (K_a values $\leq 0.2 \times 10^6 \text{ M}^{-1}$).

(b) *In vitro* studies in the isolated mouse hemidiaphragm nerve-muscle preparation

In the isolated mouse hemidiaphragm, a 90% neuromuscular block (a 90% block of twitch height) was produced by various neuromuscular blocking agents. The sugammadex concentrations causing a 50% recovery of twitch height (EC_{50}) for the steroidal neuromuscular blocking agents, pipecuronium, rocuronium, vecuronium, and pancuronium, were 0.1 ± 0.0 , 1.2 ± 0.8 , 0.8 ± 0.1 , and $1.2 \pm 0.3 \text{ }\mu\text{M}$, respectively, the maximum reversal of neuromuscular block was $91.1 \pm 1.8\%$, $95.1 \pm 2.3\%$, $90.6 \pm 5.1\%$, and $60.4 \pm 8.7\%$, respectively, and the ratio between the EC_{50} of sugammadex and the EC_{90} of the neuromuscular blocking agent was 0.3 ± 0.0 , 0.3 ± 0.2 , 0.9 ± 0.2 , and 1.3 ± 0.3 , respectively. The maximum reversal of suxamethonium (a non-steroidal neuromuscular blocking agent)-induced neuromuscular block by sugammadex was $24.5 \pm 8.8\%$ and the EC_{50} could not be calculated. Both sugammadex ($3.6 \text{ }\mu\text{M}$) and neostigmine ($7.0 \text{ }\mu\text{M}$) reversed rocuronium (EC_{90} , $3.6 \text{ }\mu\text{M}$)-induced neuromuscular block. Sugammadex ($3.6 \text{ }\mu\text{M}$) reversed neuromuscular block induced by a high concentration of rocuronium (3 times the EC_{90} [$3 \times EC_{90}$], $10.8 \text{ }\mu\text{M}$). In contrast, neostigmine (7.0 - $9.0 \text{ }\mu\text{M}$) did not reverse it.

(c) *In vivo* studies in the gastrocnemius muscle of anesthetized rats

A neuromuscular block was produced in the gastrocnemius muscle of rats by rocuronium ($3 \times ED_{90}$, $3.93 \text{ }\mu\text{mol/kg}$). The time to 90% recovery of twitch height after sugammadex ($1.00 \text{ }\mu\text{mol/kg}$) or saline administration was 5.2 ± 0.8 or 12.3 ± 2.4 minutes, respectively. A neuromuscular block was produced in the gastrocnemius muscle of rats by vecuronium ($3 \times ED_{90}$, $1.25 \text{ }\mu\text{mol/kg}$). The time to 90% recovery of twitch height after sugammadex ($1.84 \text{ }\mu\text{mol/kg}$) or saline administration was 1.6 ± 0.6 or 9.1 ± 2.0 minutes, respectively.

(d) *In vivo* studies in the gastrocnemius muscle of anesthetized guinea pigs

Rocuronium or vecuronium was given to guinea pigs to produce a 90% block of the gastrocnemius muscle twitch. The times to 90% recovery of twitch height after the administration of 0.06, 0.07, and 0.46 $\mu\text{mol/kg}$ of sugammadex or saline were 2.86 ± 0.36 , 1.03 ± 0.26 , 0.63 ± 0.07 , and 5.13 ± 0.54 to 6.77 ± 1.27 minutes, respectively, for rocuronium. The times to 90% recovery of twitch height after the administration of 0.06, 0.07, and 0.46 $\mu\text{mol/kg}$ of sugammadex or saline were 3.40 ± 0.49 , 1.60 ± 0.27 , 0.97 ± 0.08 , and 6.76 ± 1.19 to 21.15 ± 3.21 minutes, respectively, for vecuronium.

A neuromuscular block was produced in the gastrocnemius muscle of guinea pigs by rocuronium ($10 \times \text{ED}_{90}$, 1.692 ± 0.147 to $1.783 \pm 0.216 \mu\text{mol/kg}$). The time to 90% recovery of twitch height after sugammadex (2.3 $\mu\text{mol/kg}$) or saline administration was 8.5 ± 2.2 or 78.3 ± 15.2 minutes, respectively.

A neuromuscular block was produced in the gastrocnemius muscle of guinea pigs by rocuronium ($3 \times \text{ED}_{90}$, 0.390 ± 0.056 to $0.429 \pm 0.014 \mu\text{mol/kg}$). The time to 90% recovery of twitch height after sugammadex (0.5 $\mu\text{mol/kg}$), neostigmine¹²⁾ (0.165 $\mu\text{mol/kg}$), or saline administration was 6.1 ± 1.2 , 16.4 ± 4.1 , or 19.6 ± 1.5 minutes, respectively.

A 90% neuromuscular block (a 90% block of twitch height) was produced by various neuromuscular blocking agents. The time to 90% recovery after the administration of sugammadex (0.46 $\mu\text{mol/kg}$) was 0.63 ± 0.07 minutes and spontaneous recovery¹³⁾ took 5.13 ± 0.54 minutes for a steroidal neuromuscular blocking agent, rocuronium. The recovery times were 0.97 ± 0.08 and 21.15 ± 3.21 minutes, respectively, for a steroidal neuromuscular blocking agent, vecuronium, and 0.78 ± 0.10 and 13.91 ± 3.39 minutes, respectively, for a steroidal neuromuscular blocking agent, pancuronium. Meanwhile, the recovery times were 9.35 ± 1.75 and 7.98 ± 0.90 minutes, respectively, for a non-steroidal neuromuscular blocking agent, suxamethonium and 10.44 ± 2.48 and 8.91 ± 0.72 minutes, respectively, for a non-steroidal neuromuscular blocking agent, *d*-tubocurarine.

(e) *In vivo* studies in the tibialis muscle of anesthetized cats

A 90% neuromuscular block (a 90% block of twitch height) was produced in the tibialis muscle of cats by rocuronium. The time to 90% recovery of twitch height after sugammadex (0.46

¹²⁾ In order to reduce the cholinomimetic effects of neostigmine, atropine was administered at 1 minute before the administration of neostigmine.

¹³⁾ Saline was not administered and the time to recovery from neuromuscular block was calculated from the time of stopping continuous infusion of a neuromuscular blocking agent as the starting point.

$\mu\text{mol/kg}$) or saline administration was 2.2 ± 0.5 or 9.2 ± 2.9 minutes, respectively, and the time to 90% recovery of twitch height after neostigmine ($0.0801 \mu\text{mol/kg}$)¹²⁾ or saline administration was 4.8 ± 1.4 or 8.4 ± 1.9 minutes, respectively.

(f) *In vivo* studies in the adductor pollicis muscle of anesthetized monkeys

A 90% neuromuscular block (a 90% block of twitch height) was produced in the adductor pollicis muscle of monkeys by rocuronium. The time to 90% recovery of twitch height after sugammadex ($0.46 \mu\text{mol/kg}$) or saline administration was 2.9 ± 1.3 or 16.5 ± 3.5 minutes, respectively, and the time to 90% recovery of twitch height after neostigmine ($0.132 \mu\text{mol/kg}$)¹²⁾ or saline administration was 6.2 ± 1.0 or 10.2 ± 1.3 minutes, respectively.

A 90% neuromuscular block (a 90% block of T_1 of TOF¹⁴⁾) was produced in the adductor pollicis muscle of monkeys by various neuromuscular blocking agents. The times to recovery of the T_4/T_1 ratio to 0.9 after the administration of sugammadex (0.23 and $0.46 \mu\text{mol/kg}$) and the time to spontaneous recovery¹³⁾ of the T_4/T_1 ratio to 0.9 were 3.7 ± 1.6 , 1.9 ± 0.5 , and 14.5 ± 1.1 to 15.4 ± 2.2 minutes, respectively, for rocuronium, 16.5 ± 4.1 , 4.4 ± 0.6 , and 23.1 ± 1.8 to 25.0 ± 2.8 minutes, respectively, for vecuronium, 2.5 ± 0.5 , 2.5 ± 0.9 , and 18.6 ± 2.3 to 19.0 ± 3.6 minutes, respectively, for 3-OH-vecuronium, and 31.2 ± 6.3 , 19.7 ± 7.0 , and 34.2 ± 4.9 to 37.6 ± 5.6 minutes, respectively, for pancuronium.

A neuromuscular block was produced in the adductor pollicis muscle of monkeys by rocuronium, vecuronium, or pancuronium ($5 \times \text{ED}_{90}$, 0.80 ± 0.02 , 0.07 ± 0.004 , or $0.055 \pm 0.003 \mu\text{mol/kg}$, respectively). The time to recovery of the T_4/T_1 ratio to 0.9 after sugammadex ($1.15 \mu\text{mol/kg}$) or saline administration was 7.9 ± 1.8 or 28.2 ± 3.4 minutes, respectively, for rocuronium, 48.6 ± 8.3 or 49.0 ± 4.7 minutes, respectively, for vecuronium, and 89.0 ± 6.7 or 101.4 ± 6.7 minutes, respectively, for pancuronium.

A neuromuscular block was produced in the adductor pollicis muscle of monkeys by $2 \times$ human ED_{90} ¹⁵⁾ dose of rocuronium or vecuronium (0.984 or $0.157 \mu\text{mol/kg}$, respectively). The time to recovery of the T_4/T_1 ratio to 0.9 after sugammadex or saline administration was 8.4 ± 2.1 minutes with $0.918 \mu\text{mol/kg}$ of sugammadex, 5.5 ± 0.6 minutes with $1.836 \mu\text{mol/kg}$ of sugammadex, and 28.6 ± 2.0 minutes with saline for rocuronium and 74.1 ± 6.4 minutes with $1.836 \mu\text{mol/kg}$ of sugammadex, 66.8 ± 13.8 minutes with $3.672 \mu\text{mol/kg}$ of sugammadex, $8.1 \pm$

¹⁴⁾ The T_4/T_1 ratio is a measure of the depth of neuromuscular blockade. The T_4/T_1 ratio is the ratio of the amplitude of the fourth response (T_4) over that of the first response (T_1) of the TOF (train-of-four: four consecutive square wave supra-maximal stimuli of 0.2 msec. duration delivered at a frequency of 2 Hz). At complete recovery, the T_4/T_1 ratio is approximately 1.0.

¹⁵⁾ Human ED_{90} was determined based on the published literature (rocuronium, Agoston S et al. *Anesth Analg*. 1986;27:31-48, vecuronium, Bowman WC et al. *Excerpta Medica*. 1990;182-193.).

0.8 minutes with 14.688 $\mu\text{mol/kg}$ of sugammadex, and 80.4 ± 8.3 minutes with saline for vecuronium.

3.(i).A.(1).2) Studies on primary pharmacodynamics of sugammadex-related γ -cyclodextrins (4.2.1.1.2)

Among Related Substance Org 48302 that is handled as an active substance together with sugammadex in the specification for the drug substance or drug product [see “2. Data relating to quality”] and [REDACTED] 18 different related substances (Related Substance A, Org48301, Related Substance B, Related Substance C, Related Substance D, Related Substance K-1, Related Substance E, Related Substance F, Related Substance G, Related Substance H, Related Substance I, Related Substance J, Related Substance L-1, Related Substance N, Related Substance M-1, Related Substance K-2, Related Substance M-2, Related Substance L-2), the primary pharmacodynamics of 17 different related substances were investigated.¹⁶⁾ Related Substance M-2 and Related Substance L-2 were excluded since they could not be purified in enough quantities to perform studies.

The K_a value of Related Substance Org48302 with rocuronium or vecuronium, as determined by isothermal microcalorimetry, was 8.21 ± 0.12 or $4.68 \pm 0.34 \times 10^6 \text{ M}^{-1}$, respectively, and the K_a values of other related substances with rocuronium or vecuronium were 0.18 ± 0.01 to 124.72 ± 44.06 or 0.10 ± 0.01 to $59.60 \pm 11.71 \times 10^6 \text{ M}^{-1}$, respectively.

In the *in vitro* isolated mouse hemidiaphragm, the EC_{50} value of Org48302 for reversing a neuromuscular block induced by rocuronium (EC_{90} , 3.6 μM) or vecuronium (EC_{100} , 1.0 μM) was 1.24 ± 0.16 or $1.04 \pm 0.06 \mu\text{M}$, respectively, and Related Substance K-1, Related Substance J, Related Substance N, and Related Substance K-2 were weakly active in reversing the action of vecuronium and their EC_{50} values were not calculated and the EC_{50} values of other related substances were 0.56 ± 0.09 to 5.77 ± 0.46 or 0.27 ± 0.03 to $4.38 \pm 0.35 \mu\text{M}$, respectively. The maximum reversal of rocuronium- or vecuronium-induced neuromuscular block by Org48302 was $98.2 \pm 4.1\%$ or $74.9 \pm 3.9\%$, respectively.

A neuromuscular block was produced in the *in vivo* gastrocnemius muscle of guinea pigs by rocuronium ($3 \times ED_{90}$, 0.4 $\mu\text{mol/kg}$). The times to 90% recovery of twitch height after the administration of various related substances (all 0.5 $\mu\text{mol/kg}$) were 3.3 ± 1.3 minutes with

¹⁶⁾ Related Substance N, Related Substance M-1, and Related Substance K-2 (all in the heptasodium salt form) were identified after regulatory submission and primary pharmacodynamic studies were conducted using Related Substance N (the pentasodium salt), Related Substance M-1 (the free acid), and Related Substance K-2 (the monosodium salt) of different salt forms, but determination of the affinity for vecuronium using isothermal microcalorimetry or an *in vivo* study in the gastrocnemius muscle of anesthetized guinea pigs has not been performed.

Org48302 and 0.9 ± 0.2 to 26.3 ± 6.9 minutes with other related substances.

A mixture of sugammadex and Org48302 (the ratio of sugammadex to Org48302 = 80 : 20) showed both reversal activity and the recovery times comparable to those of sugammadex alone against a rocuronium (EC_{90} , 3.6 μ M)-induced neuromuscular block in the *in vitro* mouse hemidiaphragm and against a neuromuscular block induced by rocuronium ($3 \times ED_{90}$, 0.4 μ mol/kg) or vecuronium ($4 \times ED_{90}$, 0.06 μ mol/kg) in the *in vivo* gastrocnemius muscle of guinea pigs.

3.(i).A.(1).3) Action of non-steroidal neuromuscular blocking agent after reversal of rocuronium-induced neuromuscular block with sugammadex (4.2.1.1.1)

In the *in vitro* isolated mouse hemidiaphragm, after complete reversal of rocuronium (EC_{100} , 4.0 μ M)-induced neuromuscular block with sugammadex (4.0 μ M), the EC_{50} of a non-steroidal neuromuscular blocking agent, suxamethonium was 8.35 ± 1.39 μ M, i.e. suxamethonium caused a more intense neuromuscular blockade, compared with the control group treated with the depolarizing neuromuscular blocking agent only¹⁷⁾ (23.51 ± 4.10).

In the *in vivo* gastrocnemius muscle of anesthetized guinea pigs, after complete reversal of rocuronium ($3 \times ED_{90}$, 0.43 μ mol/kg)-induced neuromuscular block with sugammadex (0.5 μ mol/kg), the time to onset of suxamethonium ($2 \times ED_{90}$, 0.65 μ mol/kg) neuromuscular block was 3.0 ± 0.2 minutes, which was increased compared with the control group¹⁷⁾ (1.2 ± 0.5 minutes).

3.(i).A.(1).4) Studies investigating influences on reversal of neuromuscular blockade by sugammadex (4.2.1.1.1)

(a) Influence of magnesium

In the *in vitro* isolated mouse hemidiaphragm, after complete reversal of rocuronium (EC_{100} , 4.0 μ M)-induced neuromuscular block with sugammadex (3.9 μ M), a 3.5 mM increase in the magnesium concentration of the buffer resulted in re-occurrence of blockade ($12.0 \pm 6.9\%$ of baseline twitch height). When reversed by a high dose of sugammadex (5.6-19.0 μ M), an increase in the magnesium concentration did not cause re-occurrence of blockade ($60.0 \pm 4.0\%$ to $73.7 \pm 0.9\%$ of baseline twitch height).

In the *in vivo* gastrocnemius muscle of anesthetized guinea pigs, after complete reversal of rocuronium ($3 \times ED_{90}$, 0.43 μ mol/kg)-induced neuromuscular block with sugammadex (0.33

¹⁷⁾ The control group was treated with two doses of distilled water, instead of rocuronium and sugammadex.

and $0.66 \mu\text{mol/kg}$), intravenous administration of magnesium sulfate ($720 \mu\text{mol/kg}$) resulted in re-occurrence of blockade ($2.1 \pm 1.3\%$ and $18.5 \pm 6.5\%$ of baseline twitch height, respectively) and the times to 90% recovery of twitch height after the administration of magnesium sulfate were 34.4 ± 1.8 and 13.2 ± 3.2 minutes, respectively.

(b) Influence of antibiotics

In the *in vitro* isolated mouse hemidiaphragm, after complete reversal of rocuronium (EC_{100} , $4.0 \mu\text{M}$)-induced neuromuscular block with sugammadex ($3.9 \mu\text{M}$), the addition of neomycin or streptomycin (both $300 \mu\text{M}$) resulted in re-occurrence of blockade (T_4/T_1 ratio¹⁴) was 0.51 ± 0.07 or 0.56 ± 0.06 , respectively). When reversed by a high dose of sugammadex ($5.4 \mu\text{M}$), the addition of neomycin or streptomycin did not cause re-occurrence of blockade (T_4/T_1 ratio was 0.97 ± 0.09 or 0.96 ± 0.02 , respectively).

In the *in vivo* gastrocnemius muscle of anesthetized guinea pigs, after complete reversal of rocuronium ($3 \times \text{ED}_{90}$, $0.43 \mu\text{mol/kg}$)-induced neuromuscular block with sugammadex (0.31 and $0.63 \mu\text{mol/kg}$), intravenous administration of neomycin ($40 \mu\text{mol/kg}$) resulted in re-occurrence of blockade ($10.2 \pm 6.3\%$ and $50.2 \pm 11.3\%$ of baseline twitch height, respectively) and the times to 90% recovery of twitch height after neomycin administration were 12.4 ± 0.4 and 3.9 ± 0.9 minutes, respectively.

(c) Influence of acid-base imbalances

A neuromuscular block was produced in the *in vivo* gastrocnemius muscle of guinea pigs by rocuronium (ED_{90} , $0.155 \mu\text{mol/kg}$). The time to 90% recovery of twitch height after sugammadex ($0.46 \mu\text{mol/kg}$) administration was not affected by the condition of respiratory acidosis or alkalosis (ventilatory frequency, 20/min or 100/min, respectively) or metabolic acidosis or alkalosis (0.6 M lactic acid or 0.6 M sodium bicarbonate, respectively), was given as a continuous intravenous infusion at a rate of $250 \mu\text{L/min}$.

(d) Influence of decreased renal blood flow

A 90% neuromuscular block (a 90% block of twitch height) was produced in the *in vivo* gastrocnemius muscle of guinea pigs by rocuronium. There were no major differences in the time to 90% recovery of twitch height after the administration of sugammadex (0.069 , 0.23 , $0.46 \mu\text{mol/kg}$) between one renal artery-ligated and untreated guinea pigs.

A neuromuscular block was produced in the *in vivo* tibialis muscle of cats with both renal arteries ligated by rocuronium ($2 \times \text{ED}_{90}$, $0.82 \mu\text{mol/kg}$). The time to 90% recovery of twitch

height after sugammadex (2.3 $\mu\text{mol/kg}$) administration was 4.6 ± 0.2 minutes and the time to spontaneous recovery¹³⁾ to 90% twitch height was 31.2 ± 5.3 minutes.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1 Studies on secondary pharmacodynamics of sugammadex (4.2.1.1.1)

Sugammadex (36 μM) had no effect on the height of twitches evoked by constant-current field stimulation in the *in vitro* isolated mouse hemidiaphragm nerve-muscle and isolated mouse vas deferens preparations. Sugammadex (36 μM) had also no effect on rat aortic ring contractions induced by adrenaline (10^{-10} to 10^{-5} M), noradrenaline (10^{-10} to 10^{-5} M), serotonin (10^{-8} to 10^{-4} M), dopamine (10^{-8} to 10^{-4} M), and histamine (10^{-5} to 10^{-2} M), or guinea pig second tracheal ring contractions induced by acetylcholine (10^{-8} to 10^{-3} M) and histamine (10^{-7} to 10^{-3} M).

Sugammadex (3-100 μM) had no effects on resting tension or twitches evoked by constant-current field stimulation in the *in vitro* isolated rat iliac arteries. Sugammadex (0.1-100 μM) had no effect on the isolated spontaneously beating guinea pig right atrium *in vitro* and sugammadex (72 μM) had no effect on the acetylcholine (10^{-9} to 10^{-4} M)- or methacholine (10^{-8} to 10^{-4} M)-induced decrease in heart rate.

In *in vivo* primary pharmacodynamic studies in anesthetized rats, anesthetized guinea pigs, anesthetized cats, and anesthetized monkeys [see “3.(i).A.(1).1) Studies on primary pharmacodynamics of sugammadex”], sugammadex did not affect blood pressure or heart rate.

3.(i).A.(2).2 Studies on secondary pharmacodynamics of sugammadex-related γ -cyclodextrins (4.2.1.1.2)

In an *in vivo* primary pharmacodynamic study in anesthetized guinea pigs [see “3.(i).A.(1).2) Studies on primary pharmacodynamics of sugammadex-related γ -cyclodextrins”], 14 different related substances including Org 48302 (all 0.5 $\mu\text{mol/kg}$) had no effects on blood pressure or heart rate.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1 Effect on action potential in isolated canine Purkinje fibers (4.2.1.3.1, 4.2.1.3.2, 4.2.1.3.3)

Both sugammadex (0.276-1500 μM) and Related Substance Org 48302 (15-1500 μM) at ≥ 150 μM prolonged the action potential duration (stimulus frequencies of 1 and 0.33 Hz) by $\leq 10\%$ in isolated canine Purkinje fibers and early afterdepolarization or delayed afterdepolarization did not occur.

3.(i).A.(3).2) Effect on hERG channel tail current (4.2.1.3.5)

In human embryonic kidney cells (HEK-293 cells) expressing hERG-1, sugammadex (1500 μM) inhibited the hERG tail current by $22 \pm 2\%$.¹⁸⁾

3.(i).A.(3).3) Cardiovascular effects in anesthetized dogs (4.2.1.3.6)

Rocuronium (1.8 mg/kg) was given to anesthetized dogs to produce a neuromuscular block. Transient slight increases in heart rate and coronary blood flow and a decrease in coronary vascular resistance were observed at 1 minute after the administration of 25 mg/kg sugammadex. Similar findings were observed also after the administration of rocuronium alone and were not observed after the administration of 250 mg/kg sugammadex. At 5 minutes after the administration of 250 mg/kg sugammadex, mild and transient QTc prolongation (6.9% prolongation for both QTc Bazzet and QTc Fridericia) occurred.¹⁹⁾

3.(i).A.(3).4) Respiratory effects (4.2.1.3.7)

In conscious rats, sugammadex (4.6, 23, 92 mg/kg) had no effects on respiratory rate, tidal volume, expiratory volume, pulmonary flow resistance, inspiratory time, expiratory time, relaxation time, peak inspiratory flow, peak expiratory flow, end-inspiratory pause, or end-expiratory pause.

3.(i).A.(3).5) Effects on spontaneous locomotor activity and body temperature (4.2.1.3.8)

In rats, sugammadex (20, 100, 500 mg/kg) had no effects on functional observational battery (neurobehavioral and clinical findings), spontaneous locomotor activity, or body temperature.

3.(i).A.(4) Pharmacodynamic drug interactions (4.2.1.4.1)

3.(i).A.(4).1) Screening using isothermal microcalorimetry

The K_a values of sugammadex with various drugs were determined by isothermal microcalorimetry. The K_a value of sugammadex with raloxifene was $15.70 \times 10^6 \text{ M}^{-1}$ while sugammadex showed little affinity for acetaminophen, doxycycline, remifentanyl, spironolactone, naloxone, atropine, canrenoate, dobutamine, methylprednisolone, and gabexate (K_a values $\leq 0.2 \times 10^6 \text{ M}^{-1}$).

¹⁸⁾ Due to an increased osmolality of the perfusate, sugammadex at doses $\geq 1500 \mu\text{M}$ could not be tested and IC_{50} could not be calculated. Sugammadex 1500 μM is equivalent to 120, 60, and 15 times the maximum plasma concentrations in humans at 2, 4, and 16 mg/kg, respectively (25, 50, and 200 $\mu\text{g/mL}$, respectively, which were calculated conservatively using the dose-normalized mean value for maximum plasma concentrations at 1 to 16 mg/kg in Japanese and Caucasian healthy adult subjects [5.3.3.3.1, Trial 19.4.102], i.e. $11.1 (\mu\text{g/mL})/(\text{mg/kg})$).

¹⁹⁾ The maximum plasma concentration of sugammadex in dogs at 250 mg/kg is about 2000 $\mu\text{g/mL}$ (1 mM), which is equivalent to about 80, 40, and 10 times the maximum plasma concentrations in humans at 2, 4, and 16 mg/kg, respectively.

3.(i).A.(4).2) Interaction with raloxifene in *in vitro* isolated mouse hemidiaphragm nerve-muscle preparation

In the isolated mouse hemidiaphragm, after complete reversal of rocuronium or vecuronium (EC_{100} , 4.0 or 1.0 μM , respectively)-induced neuromuscular block with sugammadex (2.8 or 2.0 μM , respectively), the addition of raloxifene (7.0 μM^{20}) did not result in re-occurrence of blockade for rocuronium while blockade reoccurred for vecuronium. In the presence or absence of raloxifene, the EC_{50} value of rocuronium for neuromuscular blocking action was 4.53 ± 0.18 or 5.29 ± 0.24 μM , respectively, and the EC_{50} value of vecuronium was 0.82 ± 0.01 or 1.7 ± 0.07 μM , respectively.

3.(i).A.(4).3) Interactions with acetaminophen, doxycycline, remifentanyl, spironolactone, and carbachol in *in vitro* isolated mouse hemidiaphragm nerve-muscle preparation

In the isolated mouse hemidiaphragm, after almost complete reversal of rocuronium (EC_{100} , 4.0 μM)-induced neuromuscular block with sugammadex (2.8 μM) (77.7 ± 8.8 to $89.4 \pm 3.0\%$ of baseline twitch height), the addition of a high dose of acetaminophen (4000 μM), doxycycline (100 μM), remifentanyl (1 μM), or spironolactone (7.5 μM) did not result in re-occurrence of blockade.

In the isolated mouse vas deferens, remifentanyl (0.1 μM)-induced neuromuscular block ($21.3 \pm 3.1\%$ of baseline twitch height) was not reversed by sugammadex (100 μM), but partially reversed by naloxone (0.1 μM) ($62.1 \pm 2.6\%$ of baseline twitch height). After reversal of remifentanyl-induced neuromuscular block with naloxone ($71.6 \pm 1.6\%$ of baseline twitch height), the addition of sugammadex (100 μM) resulted in re-occurrence of blockade ($54.5 \pm 3.6\%$ of baseline twitch height).

Carbachol (30 μM , unapproved in Japan)-induced contractions of isolated rat tracheal rings were antagonized by atropine (30 nM), but not affected by sugammadex (100 μM). Sugammadex had no effect on the antagonism of carbachol-induced muscle contractions by atropine.

3.(i).A.(4).4) Interactions with remifentanyl, naloxone, dobutamine, canrenoate, methylprednisolone, and gabexate in *in vivo* gastrocnemius muscle of anesthetized rats

In the gastrocnemius muscle of anesthetized rats, after almost complete reversal of

²⁰⁾ Due to the low solubility of raloxifene, the actual raloxifene concentration in the buffer was 1.7 to 2.2 μM , which was ≥ 480 times higher than the maximum plasma concentration in humans (about 3.5 nM).

vecuronium²¹⁾ (0.2 mg/kg/min, 15 minutes)-induced neuromuscular block with sugammadex (3.00 mg/kg) (57.9 ± 16.5% to 90.2 ± 6.5% of baseline twitch height), intravenous administration (as a bolus or a 25-minute continuous infusion) of remifentanyl (100 µg/kg/min), naloxone (5 mg/kg), dobutamine (4 mg/kg followed by 2 mg/kg/min), canrenoate (0.1 mg/kg/min), or methylprednisolone (20 mg/kg) did not result in re-occurrence of blockade²²⁾ and had no apparent effects on the recovery from the neuromuscular blockade.

A neuromuscular block was produced in the gastrocnemius muscle of anesthetized rats by vecuronium (3 × ED₉₀, 1.25 µmol/kg). The time to recovery of the T₄/T₁ ratio to 0.9 after intravenous administration of gabexate (1.5 mg/kg/h), sugammadex (1.84 µmol/kg), sugammadex in combination with gabexate, or saline was 8.45, 1.21, 1.37, or 11.73 minutes, respectively, and gabexate did not affect the reversal of the vecuronium-induced neuromuscular blockade by sugammadex.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Mode of action and binding affinity of sugammadex

PMDA asked the applicant to explain the mechanism of forming inclusion complexes.

The applicant explained as follows:

Van der Waals forces and hydrophobic interactions are important elements in the ability of cyclodextrins to form inclusion complexes. Intermolecular van der Waals forces depend on complementarity between the molecule to be included and the internal cavity of cyclodextrin in terms of the sizes and shapes, and hydrophobic interactions depend on the area of the hydrophobic region involved in interaction. Sugammadex has been developed as a reversal agent for rocuronium, and a thioether linked to a propionate group (a side chain) has been added to each glucose unit of γ-cyclodextrin to extend the hydrophobic cavity to better accommodate all steroidal rings of rocuronium, and sugammadex forms tight complexes in 1:1 ratio with rocuronium (K_a values, 15.1 × 10⁶ M⁻¹ for sugammadex, 0.0132 × 10⁶ M⁻¹ for γ-cyclodextrin) based on electrostatic binding between the negatively charged carboxyl groups at the end of the side chains and the quaternary ammonium moiety in the rocuronium molecule.

PMDA asked the applicant to explain the binding affinity of sugammadex for compounds other than rocuronium.

²¹⁾ The *in vivo* drug interaction potential was investigated using vecuronium which has a lower affinity for sugammadex than does rocuronium.

²²⁾ Following the administration of methylprednisolone, 2 of the 4 rats experienced re-occurrence of blockade, which was of short duration and mild (the mean decrease in twitch height was 17%), which did not remarkably affect the recovery time of the group as a whole.

The applicant explained as follows:

Like rocuronium, compounds that are similar in molecular size and shape to rocuronium and positively charged have the potential to form inclusion complexes with sugammadex and such compounds include vecuronium and pancuronium (K_a value, 8.8 and $2.6 \times 10^6 \text{ M}^{-1}$, respectively). Sugammadex was not developed as a reversal agent for pancuronium, since its binding affinity (K_a value) for sugammadex is lower compared with rocuronium and vecuronium and a foreign phase II trial (Trial 19.4.207) showed no statistically significant dose response of sugammadex in reversing a pancuronium-induced neuromuscular blockade. Sugammadex has a lower binding affinity for vecuronium compared with rocuronium and in an *in vivo* study in the adductor pollicis muscle of anesthetized monkeys (4.2.1.1.1), when sugammadex was administered 3 minutes after a clinical dose ($2 \times$ human ED_{90}) of rocuronium or vecuronium, assuming situations requiring immediate reversal, sugammadex reduced the time to recovery of the T_4/T_1 ratio to 0.9 for rocuronium but not for vecuronium. The reason could be explained as follows: A threshold block is associated with 70% to 80% receptor occupancy by a neuromuscular blocking agent at the neuromuscular junction (Paton WD et al. *J physiol (Lond)*. 1967;191: 59-90.) and a slight change in plasma free neuromuscular blocking agent level significantly alters the level of neuromuscular blockade at around the threshold; therefore, in the presence of a high concentration of vecuronium or rocuronium, the difference in the binding affinity with sugammadex might have affected the recovery time.

PMDA asked the applicant to explain the site of action of sugammadex in the body.

The applicant explained as follows:

Simulations using the PK/PD model (Nigrovic V et al. *J Pharmacokinet Pharmacodyn*. 2007;34:771-788.) revealed that sugammadex can produce a rapid recovery from neuromuscular blockade as seen in a clinical setting if sugammadex is postulated to diffuse between plasma and the extra-cellular space of muscle and form inclusion complexes. However, whether sugammadex penetrates the membrane of the Schwann cell separating the synaptic cleft from extracellular fluid is unknown and formation of inclusion complexes in the synaptic cleft has not been confirmed.

PMDA accepted the above.

3.(i).B.(2) Pharmacodynamic interactions and the influences on neuromuscular blockade

PMDA asked the applicant to explain drug interactions associated with formation of inclusion complexes with sugammadex.

The applicant explained about 2 possible types of interactions associated with formation of inclusion complexes as follows:

Certain drugs other than steroidal neuromuscular blocking agents could become less effective due to clathrate formation (“capturing”) interaction potential of sugammadex, and neuromuscular blockade could re-occur due to “displacement” interaction potential by binding of sugammadex with another drug which has a higher affinity for sugammadex and is present at high concentration in plasma.

Then, the applicant explained as follows:

With respect to capturing interaction potential, more than 300 different drugs (drugs that are potentially used concomitantly with sugammadex in clinical practice and drugs acting on steroid receptors [with or without a steroid skeleton]) were tested for binding affinity using isothermal microcalorimetry and for drugs with K_a values greater than the cutoff value²³⁾ ($0.025 \times 10^6 \text{ M}^{-1}$), simulations were performed using the PK/PD model. As a result, a clinically relevant interaction can not be ruled out for hormonal oral contraceptives (K_a value of etonogestrel [unapproved in Japan], $2.86 \times 10^6 \text{ M}^{-1}$; an estimated 34% decrease in the area under the plasma concentration-time curve [AUC]). With respect to displacement interaction potential, as shown in the following figure, based on K_a values and maximum plasma concentrations (C_{max}) of drugs, simulations were performed using the PK/PD model to predict T_4/T_1 ratios and drugs that lie beyond the critical line (predicted T_4/T_1 ratio ≤ 0.9) were examined. As a result, a clinically relevant interaction can not be excluded for toremifene, fusidic acid, and flucloxacillin (unapproved in Japan). Of which, toremifene and fusidic acid have been approved in Japan and a medicinal product containing fusidic acid is available as a topical preparation only (Fucidin Leo Ointment 2%) and given that the percutaneous absorption rate of sodium fusidate is 2% (Vickers CF. *Br J Dermatol.* 1969;81:9022-908.), it is very unlikely to cause an interaction with sugammadex. Therefore, it has been concluded that toremifene that carries a risk of causing a clinically relevant interaction with sugammadex should be listed in the “Interactions” section of “Precautions” of the package insert.

²³⁾ The cutoff value was selected based on the relationship between the binding affinity as determined by microcalorimetry and the effects observed in *in vitro* and *in vivo* non-clinical pharmacodynamic interaction studies (4.2.1.4.1).

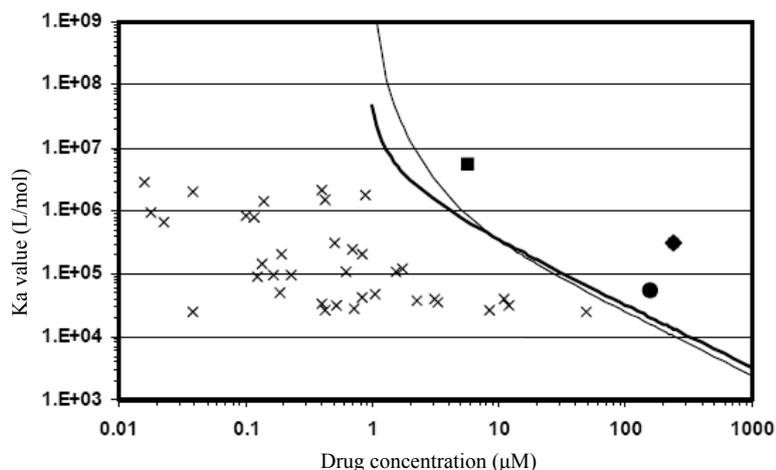


Figure. Maximum plasma concentrations and Ka values of drugs that are potentially used concomitantly with sugammadex (■: toremifene, ●: flucloxacillin, ◆: fusidic acid, ×: other drugs analyzed). Curves represent the critical lines for a T_4/T_1 ratio of 0.9 due to displacement of rocuronium [thick line] and of vecuronium [thin line] based on simulations)

The applicant also explained as follows:

Since endogenous and exogenous steroid hormones (aldosterone, progesterone, estradiol, testosterone, cortisol, cortisone, methylprednisolone) other than hormonal oral contraceptives all have low Ka values for sugammadex as determined by isothermal microcalorimetry, it is unlikely that these steroid hormones become less effective due to capturing interaction potential. In the rat and dog 4-week repeat-dose toxicity studies (4.2.3.2.4, 4.2.3.2.6) and the rat and rabbit reproductive and developmental toxicity studies (4.2.3.5.1.1, 4.2.3.5.2.1, 4.2.3.5.2.2, 4.2.3.5.3.1, 4.2.3.5.3.3), effects on plasma testosterone or estradiol levels, e.g. adrenal effects affecting endogenous steroid hormone activity, abortion, or decreased fertility, were not observed.

PMDA asked the applicant to explain drugs that may cause re-occurrence of blockade.

The applicant explained as follows:

Even when rocuronium- or vecuronium-induced neuromuscular blockade has been reversed completely by sugammadex, the receptor occupancy by the neuromuscular blocking agent at the neuromuscular junction is around 70% [see “3.(i).B.(1) Mode of action and binding affinity of sugammadex”]. Thus, if subsequent administration of magnesium or aminoglycoside antibiotics etc. inhibits the release of acetylcholine at the neuromuscular junction, re-occurrence of blockade may occur. However, if a high dose of sugammadex further lowers the receptor occupancy by a neuromuscular blocking agent, re-occurrence of blockade can be prevented [see “3.(i).A.(1).4) Studies investigating influences on reversal of neuromuscular blockade by sugammadex”]. In Japanese and foreign clinical trials, none of 68 subjects who received

magnesium²⁴⁾ experienced an adverse event associated with prolonged neuromuscular blockade, or recurarization or a prolonged neuromuscular blocking effect based on neuromuscular monitoring. Drugs affecting neuromuscular blockade are widely known (*Miller's Anesthesia*. 2007;383-452. Takeda J spv.ed. Tokyo, Medical Sciences International, Ltd.) and precautions have been provided in the package inserts for neuromuscular blocking agents. In clinical practice, re-occurrence of blockade can be prevented by complying with the labeled dosage and administration instructions for sugammadex and appropriately monitoring the status of neuromuscular blockade. In the "Important precautions" section of "Precautions" of the package insert, the use of a neuromuscular monitor will be advised. It will also be advised to refer to the "Interactions" section of the package insert for rocuronium or vecuronium and pay a special attention to the possibility of re-occurrence of blockade when drugs which potentiate neuromuscular blockade are used in the postoperative period.

PMDA considered that appropriate precautions about potential pharmacological interactions are provided and accepted the applicant's explanation.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The results from absorption, distribution, metabolism, and excretion studies in rats, guinea pigs, rabbits, dogs, and cats were submitted. Doses are expressed as the free acid. Plasma levels of sugammadex (unchanged sugammadex), Related Substance Org48302, which is an active substance [see "2. Data relating to quality"], and rocuronium were determined by liquid chromatography-mass spectrometry (LC-MS) according to validated procedures²⁵⁾ (Lower limit of quantification for unchanged sugammadex, 183-7130 ng/mL for rats, 2000 ng/mL for rabbits, 91.6-1000 ng/mL for dogs, 410 ng/mL for cats; Lower limit of quantification for Org48302, 200 ng/mL for rats; Lower limit of quantification for rocuronium, 9.56-100 ng/mL for dogs, 19.1 ng/mL for cats). In studies using ¹⁴C-labeled sugammadex, radioactivity levels were determined by liquid scintillation counter (Lower limit of quantification, two times the background radioactivity). Since complex-bound and non-complex-bound concentrations can not be determined separately using these analytical methods, pharmacokinetic parameters were calculated from the total sum of complex-bound and non-complex-bound concentrations of unchanged sugammadex, Related Substance Org48302, or rocuronium, and are expressed as the mean ± standard deviation (SD), unless otherwise specified. Unless otherwise specified, doses

²⁴⁾ As concomitant use of aminoglycoside antibiotics was prohibited in Japanese and foreign clinical trials, there were no subjects who received aminoglycoside antibiotics.

²⁵⁾ Although an assay for determination of rocuronium concentrations in a guinea pig pharmacology study has not been validated under GLP, it has been confirmed that rocuronium can be assayed appropriately with a lower limit of quantification of 25 ng/mL (Epemolu O et al. *Rapid Commun Mass Spectrom*. 2002;16:1946-1952.).

of sugammadex are expressed as the free acid.

3.(ii).A.(1) Absorption

Pharmacokinetic parameters of unchanged sugammadex and Org48302 in plasma following single intravenous doses of 120, 500, and 2000 mg/kg of sugammadex (Drug substance batch AE containing █% of Related Substance Org48302) in male and female rats were as shown in the following table. There were no gender-related differences, the elimination half-lives ($t_{1/2}$) of sugammadex and Org48302 were almost constant regardless of dose, and there were no major differences between the two compounds (4.2.2.2.1).

Table. Pharmacokinetic parameters of unchanged sugammadex and Org48302 in plasma following single intravenous doses of sugammadex in rats

Pharmacokinetic parameter	Dose					
	Sugammadex 120 mg/kg (Org48302 █ mg/kg)		Sugammadex 500 mg/kg (Org48302 █ mg/kg)		Sugammadex 2000 mg/kg (Org48302 █ mg/kg)	
	Male	Female	Male	Female	Male	Female
Unchanged sugammadex						
AUC _{0-∞} (µg·h/mL)	156	175	665	744	4699	3581
$t_{1/2}$ (h)	0.37	0.44	0.45	0.72	0.50	0.46
CL (L/h/kg)	0.77	0.69	0.75	0.67	0.43	0.56
V (L/kg)	0.41	0.43	0.49	0.70	0.31	0.37
Org48302						
AUC _{0-∞} (µg·h/mL)	12.7	13.9	54.4	62.8	438	339
$t_{1/2}$ (h)	0.39	0.33	0.36	0.61	0.69	0.40
CL (L/h/kg)	0.57	0.52	0.55	0.48	0.27	0.35
V (L/kg)	0.32	0.25	0.29	0.42	0.27	0.21

n = 2: 6 males and 6 females were treated and blood was collected from 2 males and 2 females at each timepoint.

Following a single intravenous dose of 8 mg/kg of ¹⁴C-sugammadex in male and female rats, the AUC_{last} of plasma radioactivity was 12.17 and 17.44 µg eq·h/g, respectively, the terminal elimination half life ($t_{1/2\beta}$)²⁶⁾ was 15 and 14 hours, respectively, and the clearance (CL)²⁶⁾ was 0.649 and 0.460 L/h/kg, respectively. Following a single intravenous dose of 2 mg/kg of ³H-rocuronium alone or followed by a single intravenous dose of 8 mg/kg of sugammadex 5 minutes later in male and female rats, there were no gender-related differences in the pharmacokinetic parameters of plasma radioactivity and coadministration with sugammadex resulted in an about 1.5-fold increase in the AUC_{last} of plasma radioactivity compared with ³H-rocuronium alone (4.2.2.5.1).

Following a single intravenous dose of 8 mg/kg of ¹⁴C-sugammadex in male and female dogs, there were no major differences in the pharmacokinetic parameters between males and females and the AUC_{last} of plasma radioactivity was 31.75 ± 3.55 and 33.81 ± 3.36 µg eq·h/mL, respectively, the $t_{1/2\beta}$ ²⁶⁾ was 7.8 and 8.2 hours, respectively, and the CL²⁶⁾ was 0.250 ± 0.027 and

²⁶⁾ The elimination rate constant could not be calculated according to the protocol-specified criteria for calculating accurate pharmacokinetic parameters. Thus, the elimination rate constant and pharmacokinetic parameters obtained using this value are presented as rough estimates.

0.237 ± 0.017 L/h/kg, respectively (4.2.2.5.2). The CL values after administration of ¹⁴C-sugammadex to rats and dogs were lower than the hepatic and renal blood flow rates reported in the published article (Walton K et al. *Food Chem Toxicol.* 2004;42:261-274.) (3.3 and 2.2 L/h/kg, respectively, in rats, 1.9 and 1.3 L/h/kg, respectively, in dogs), but the CL was higher than GFR in rats and similar to GFR in dogs (0.3 L/h/kg in rats, 0.4 L/h/kg in dogs).

Following intravenous administration of 1.08 mg/kg rocuronium and 2.76 or 27.6 mg/kg sugammadex in three divided doses separated by 30 minutes (sugammadex was administered at 2 minutes after the administration of rocuronium) to male and female dogs and following intravenous administration of 1.5 mg/kg rocuronium and 2.76 or 27.6 mg/kg sugammadex in three divided doses separated by 30 minutes (sugammadex was administered at 2 minutes after the administration of rocuronium) to male and female cats, rocuronium did not affect the pharmacokinetics of unchanged sugammadex in plasma (4.2.3.1.9, 4.2.3.1.11).

Sugammadex (1.84, 7.36, 27.6 mg/kg) was intravenously administered once daily for 8 days to male and female rats. There were no gender-related differences in the pharmacokinetic parameters and the AUC_{0-∞} ratio (Day 8/Day 1) was 0.84 to 1.23²⁷⁾ and the t_{1/2} was 0.21 to 0.37 hours and there were no major differences between single- and repeat-dose pharmacokinetics of unchanged sugammadex in plasma (4.2.3.2.1). Sugammadex (30, 120, 500 mg/kg) was intravenously administered once daily for 3 weeks to male and female rats (4.2.3.2.3), sugammadex (1.8, 7.4, 27.6 mg/kg) was intravenously administered for 2 weeks to male and female dogs (4.2.3.2.5), and sugammadex (25, 80, and 250 mg/kg) was intravenously administered once daily for 3 weeks to male and female dogs (4.2.2.2.2), and the pharmacokinetic parameters of unchanged sugammadex in plasma were determined. As a result, it was found that the pharmacokinetics of unchanged sugammadex in plasma were not affected by repeated administration.

Sugammadex (20, 65, 200 mg/kg) was intravenously administered once daily for 9 days to white rabbits on gestation day 14. The AUC_{0-∞} was 100.5, 403.7, and 1400.8 µg·h/mL, respectively (4.2.3.5.2.2).

Sugammadex (30, 120, 500 mg/kg) was subcutaneously administered as a single dose and once daily for 2 weeks to male and female juvenile rats. There were no gender-related differences in

²⁷⁾ Female rats in the 27.6 mg/kg group had abnormally low plasma levels of unchanged sugammadex after repeated administration and the AUC_{0-∞} ratio (Day 8/Day 1) was 0.14 and the test records were reviewed. As a result, it was found that there had been errors in the preparation of drug solution for this group over several days and it has been concluded that this group may have received a drug solution at a lower concentration than specified.

the pharmacokinetics of sugammadex, and the plasma levels of unchanged sugammadex after repeated administration were lower than those after single administration, which has been discussed to be attributable to increasing GFR with the age of juvenile rats (Zoetis T et al. *Birth Defects Research(part B)*. 2003;68:111-120.) (4.2.3.5.4.3).

Sugammadex (30, 120, 500 mg/kg) was administered once daily for 4 weeks (2-week subcutaneous administration followed by 2-week intravenous administration) to male and female juvenile rats. There were no gender-related differences in the pharmacokinetics of sugammadex and the AUC_{0-3hr} of plasma sugammadex after repeated intravenous administration increased almost dose-dependently (4.2.3.5.4.4).

Following a single intravenous dose of 0.36 mg/kg of 3H -rocuronium alone or followed by a single intravenous dose of 8 mg/kg of sugammadex 10 minutes later in male and female dogs, there were no gender-related differences in the pharmacokinetic parameters of plasma radioactivity and coadministration with sugammadex increased the AUC_{last} of plasma radioactivity by about 2-fold and decreased the CL and the volume of distribution (V_{ss}) to about 1/2 and 1/3, respectively, compared with 3H -rocuronium alone (4.2.2.5.2).

Male guinea pigs received sugammadex (0.1 mg/kg/min) as a 30-minute continuous intravenous infusion at 30 minutes after the start of a 60-minute continuous intravenous infusion of rocuronium (0.006 μ g/kg/min) to maintain a 90% neuromuscular block under anesthesia. The plasma rocuronium concentrations were 0.899 ± 0.497 μ g/mL immediately before the administration of sugammadex and 1.379 ± 0.472 μ g/mL at 10 minutes, 1.640 ± 0.563 μ g/mL at 20 minutes, and 1.833 ± 0.501 μ g/mL at 30 minutes after the administration of sugammadex (4.2.1.1.1), indicating that the plasma rocuronium concentration increased following the administration of sugammadex.

3.(ii).A.(2) Distribution

A single intravenous dose of 8 mg/kg of ^{14}C -sugammadex was administered to male and female albino rats. Tissue radioactivity levels at 25 minutes post-dose were high in the joint (hip), bone (femur), prostate gland (males only), vagina (females only), kidneys, and bladder (12.28 ± 10.54 to 27.96 ± 2.12 μ g eq/g, 2.02- to 4.35-fold the plasma level) and the plasma radioactivity levels in males and females were 6.45 ± 0.79 and 6.08 ± 1.16 μ g eq/g, respectively. At 168 hours post-dose, while the plasma radioactivity level declined to less than 1/3000 of its peak level, radioactivity levels in most tissues excluding the brain and pituitary gland were at least 10-fold higher than the plasma level, i.e. 691- to 732-fold higher (1.38 ± 0.46 to 1.46 ± 0.25 μ g eq/g) in

the kidneys and 5445- to 10325-fold higher (10.89 ± 0.59 to 20.65 ± 2.57 $\mu\text{g eq/g}$) in the joint (hip) and bone (femur). Following a single intravenous dose of ^3H -rocuronium alone or followed by a single intravenous dose of sugammadex 5 or 15 minutes later in male and female albino rats, sugammadex had little effect on the tissue distribution of ^3H -rocuronium. Following a single intravenous dose of 8 mg/kg of ^{14}C -sugammadex in male and female pigmented rats, there were no major differences in radioactivity concentration between the pigmented and non-pigmented skin at 24 and 168 hours post-dose and there were no major differences in the ocular level of radioactivity between pigmented and albino rats. Therefore, the applicant has discussed that sugammadex has a low melanin affinity (4.2.2.5.1).

Following a single intravenous dose of 8.6 mg/kg of ^{14}C -sugammadex in male rats, concentrations of radioactivity in bone at various sites, incisors, and tracheal cartilage, expressed as the percentage of the dose per gram of tissue (extent of binding) were 1.08% to 1.89%, 0.45%, and 0.03%, respectively, at 1 day post-dose, and 0.27% to 0.40%, 0.004%, and 0.0006%, respectively, at 84 days post-dose. When male rats received a single intravenous dose of 8.6 mg/kg of sugammadex followed by a single intravenous dose of 8.6 mg/kg of ^{14}C -sugammadex, the radioactivity contents in bone at various sites, incisors, and tissue were not different from those following a single intravenous dose of 8.6 mg/kg of ^{14}C -sugammadex alone (4.2.2.3.4).

Following single intravenous doses of ^{14}C -sugammadex (30, 120, 400 mg/kg) in male and female rats, the extent of binding to bone and teeth at 1 day post-dose decreased with increasing dose. When 30 mg/kg/day of ^{14}C -sugammadex was intravenously administered once daily for 28 days to male and female rats, the extent of binding to bone and teeth decreased after 7 days of repeated administration. Following a single intravenous dose of 30 mg/kg of ^{14}C -sugammadex in juvenile, young adult, and aged rats, the extent of binding to bone at 1 day post-dose was 13.3%, 2.8%, and 0.4%, respectively, indicating that it decreased with age and the extent of binding to teeth also decreased with age. When male and female young adult rats received a single intravenous dose of 4 mg/kg of rocuronium (at a molar ratio of rocuronium to sugammadex of about 1:2) immediately after a single intravenous dose of 30 mg/kg of ^{14}C -sugammadex, the extent of binding to bone and molars decreased by about 31% to 36% and 41% to 67%, respectively, compared with ^{14}C -sugammadex alone (4.2.2.3.5).

Following a single intravenous dose of 8.6 mg/kg of ^{14}C -sugammadex in male rats, localization of radioactivity in bone was investigated by microautoradiography of non-demineralized femur and scapula at 1, 21, and 84 days post-dose. As a result, radioactivity was localized in the

periosteum and endosteum of cortical bone (or its vicinity) and the endosteum of trabecula (or its vicinity) and radioactivity was localized to areas of active bone formation at the time of administering ^{14}C -sugammadex and not to the bone formed after the administration of ^{14}C -sugammadex (4.2.2.3.6).

Following a single intravenous dose of 20 mg/kg of ^{14}C -sugammadex in rats on gestation days 11 and 16, the embryo/maternal plasma concentration ratio of radioactivity at 60 minutes post-dose was 0.55 and 0.04, respectively. When rats on gestation days 10 and 16 intravenously received 2 mg/kg of sugammadex within 3 minutes after 0.3 mg/kg of ^3H -rocuronium, the amount of ^3H -rocuronium transferred to the embryo or fetus was reduced in rats on gestation day 10 while there were no effects in rats on gestation day 16 (4.2.2.3.7).

Following single intravenous doses of ^{14}C -sugammadex (30, 500 mg/kg) in pregnant rats, the fetal/maternal blood ratio of radioactivity was 0.056 and 0.024, respectively. In the fetus, radioactivity was highly distributed in bone with the highest level in the femur (up to 0.35% of the dose per gram of fetal femur) (4.2.2.3.8).

^{14}C -sugammadex (500 mg/kg/day) was intravenously administered for 15 days to rats on gestation days 6 to 20 and autoradiograms were obtained at 1, 2, 4, 6, and 24 hours after the last dose. Most of the radioactivity detected in fetal tissues was localized in bone and excretory organs (bladder content and gastrointestinal tract) (4.2.2.3.9).

Following a single intravenous dose of 20 mg/kg of ^{14}C -sugammadex in rabbits on gestation days 10 and 17, very low transfer of radioactivity across the placenta was seen (4.2.2.3.10).

When male rat, rabbit, cat, and dog plasma was added *in vitro* with ^{14}C -sugammadex at final concentrations of 0 to 125 μM , sugammadex did not bind to plasma proteins of any species, as determined by an equilibrium dialysis method. When sugammadex (0-12.5 μM) and ^3H -rocuronium (0.24-11.1 μM) were added at a sugammadex to rocuronium ratio of 0 to 1.1, the extent of binding of ^3H -rocuronium to plasma proteins, as determined by an equilibrium dialysis method, decreased with increasing ratio of sugammadex to rocuronium and reached 0% at an almost equimolar ratio of sugammadex to rocuronium (4.2.2.3.1).

When male rat, rabbit, cat, and dog blood was added *in vitro* with ^{14}C -sugammadex at final concentrations of 0 to 250 μM , ^{14}C -sugammadex did not bind to erythrocytes (4.2.2.3.2).

Male rat hepatocytes were added with ^{14}C -sugammadex at final concentrations of 6 and 100 μM and incubated at 4°C or 37°C for 3 hours. The uptake of ^{14}C -sugammadex into rat hepatocytes was 13 and 83 pmol/mg protein, respectively, at 4°C and 20 and 95 pmol/mg protein, respectively, at 37°C (4.2.2.3.3).

3.(ii).A.(3) Metabolism

When rat hepatocytes were added *in vitro* with ^{14}C -sugammadex at a final concentration of 6 or 100 μM and incubated at 37°C for 3 hours, no metabolites were formed (4.2.2.3.3).

Following a single intravenous dose of 8 mg/kg of ^{14}C -sugammadex in male and female rats and male and female dogs, about 50% to 80% of plasma radioactivity at 1 hour post-dose was attributed to unchanged sugammadex and about [REDACTED]% each was attributed to 2 different [REDACTED] related substances (Related Substance E and Related Substance I). About 60% to 90% of radioactivity excreted in urine and feces up to 6 to 24 hours post-dose was attributed to unchanged sugammadex and 2 different [REDACTED] related substances were detected in urine as in plasma. The applicant discussed that part of 2 different [REDACTED] related substances were formed during storage or analysis of the samples²⁸⁾ (4.2.2.5.1, 4.2.2.5.2).

When 500 mg/kg of ^{14}C -sugammadex was intravenously administered once daily for 15 days to pregnant rats, most of radioactivity in amniotic fluid was associated with unchanged sugammadex (4.2.2.3.9).

3.(ii).A.(4) Excretion

Following a single intravenous dose of 8 mg/kg of ^{14}C -sugammadex in male and female rats and male and female dogs, $78.48 \pm 3.36\%$ to $78.86 \pm 3.74\%$ and $4.22 \pm 1.06\%$ to $6.82 \pm 2.72\%$ of the administered radioactivity were excreted in urine and feces, respectively, in rats up to 168 hours post-dose, and $87.20 \pm 2.05\%$ to $87.91 \pm 3.11\%$ and $0.33 \pm 0.26\%$ to $0.80 \pm 0.06\%$ of the administered radioactivity were excreted in urine and feces, respectively, in dogs up to 168 hours post-dose. Following a single intravenous dose of 2 mg/kg of ^3H -rocuronium alone or followed by a single intravenous dose of 8 mg/kg of sugammadex 5 minutes later in male and female rats and following a single intravenous dose of 0.36 mg/kg of ^3H -rocuronium alone or followed by a single intravenous dose of 8 mg/kg of sugammadex 10 minutes later in male and female dogs, coadministration with sugammadex resulted in an increase in the urinary excretion

²⁸⁾ ^{14}C -sugammadex used in the studies contained [REDACTED]% of Related Substance E and [REDACTED]% of Related Substance I and for ^{14}C -sugammadex solution stored for the same period of time as the test samples (stored in water at about 4°C), the contents of Related Substance E and Related Substance I were increased to 10.2% and 13.4%, respectively.

of radioactivity in rats and dogs and a decrease in the fecal excretion of radioactivity in dogs, compared with ³H-rocuronium alone (4.2.2.5.1, 4.2.2.5.2).

Following a single intravenous dose of 20 mg/kg of ¹⁴C-sugammadex in lactating rats on lactation day 9, the radioactivity level in milk peaked at about 30 minutes post-dose with a plasma/milk radioactivity concentration ratio of about 1 (4.2.2.5.3).

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Retention of sugammadex in bone and teeth and safety

Following a single intravenous dose of ¹⁴C-sugammadex in rats, a high level of radioactivity was distributed into and retained in bone and teeth. PMDA asked the applicant to explain the safety of sugammadex in humans for effects on bone and teeth.

The applicant explained as follows:

Sugammadex does not bind to non-mineralized tissues (4.2.2.3.4) and preferentially binds to the sites of teeth and bone formation or mineralization, but does not bind to the epiphyseal plate, which is important for bone growth (4.2.2.3.6). As its mechanism of binding, γ -cyclodextrin has not been shown to bind to teeth or bone (De Bie ATHJ et al. *Regul Toxicol Pharmacol.* 1998;27: 150-158.), and therefore the properties of sugammadex as a polycarboxylic acid are considered to be associated with its binding to extracellular hydroxyapatite. On this base, following a single intravenous dose of 8.6 mg/kg of ¹⁴C-sugammadex (4.2.2.3.4), radioactivity levels in bone at various sites and incisors declined as shown in the following figure, and when 30 mg/kg of ¹⁴C-sugammadex was administered once daily for 28 days (4.2.2.3.5), the extent of binding to bone at various sites and incisors peaked at 1 or 3 days after the start of administration (0.60%-1.26% and 0.31%-0.32%, respectively) and declined slowly after 7 days of administration.

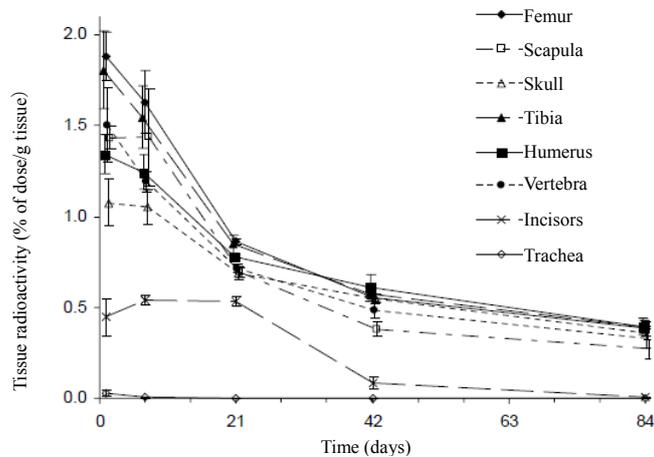


Figure. Radioactivity levels over time following a single intravenous dose of 8.6 mg/kg of ¹⁴C-sugammadex in male rats (4.2.2.3.4)

The applicant also explained as follows:

Following a single intravenous dose of 2000 mg/kg of sugammadex in rats (4.2.3.7.7.1), there were no abnormalities in the incisors and a slight bone resorptive effect in the trabecula of femur was observed, which was reversed after drug withdrawal and there was no effect on bone quality, bone structure, or bone turnover. Therefore, the slight resorptive effect observed in the trabecula of femur is considered associated with a transient surge in blood PTH noted in the rat and dog (4.2.3.7.7.3, 4.2.2.2.2). Following 4-week repeated administration of 120 to 500 mg/kg/day of sugammadex in juvenile rats (2-week subcutaneous administration followed by 2-week intravenous administration) (4.2.3.5.4.4), mild retardation of femur growth, decay in the enamel surface of the incisors, and deposition of amorphous substances were observed. However, the retardation of femur growth is considered secondary to mild growth retardation because it occurred in association with reduced body weight gain. In juvenile rat single intravenous dose toxicity studies (4.2.3.5.4.1, 4.2.3.5.4.2) and a rat 4-week repeated intravenous dose toxicity study (4.2.3.2.4), there were no apparent effects on bone or teeth. In a rat embryo-fetal development study (4.2.3.5.2.1), a skeletal malformation or an abnormal skeletal development was not noted. The rat-to-human safety margins of sugammadex for effects on bone and teeth are as shown in the following table and the conservative estimates of safety margins relative to human exposure after a single 16 mg/kg intravenous dose are ≥ 2.6 . Therefore, a single dose of sugammadex is unlikely to affect bone and teeth in humans.

Table. No observed adverse effect levels (NOAELs) of sugammadex for effects on bone and teeth and rat-to-human safety margins

		NOAEL (mg/kg)	AUC _{0-∞} (µg·h/mL)	C _{max} or C ₀ (µg/mL)	Skeletal exposure (µg/g)	Teeth exposure (µg/g)
Effect on mature rat bone	Single dose	500 ^{a)}	1050 ^{e)}	6000 ^{e)}	313 ^{g)}	- ^{k)}
	4-week repeated administration	500 ^{b)}	1050 ^{e)}	6000 ^{e)}	5000 ^{h)}	- ^{k)}
Effects on juvenile rat bone and teeth	Single dose	500 ^{c)}	432-1275 ^{f)}	580-1800 ^{f)}	150 ⁱ⁾	220 ⁱ⁾
	4-week repeated administration	30 ^{d)}	22 ^{d)}	85 ^{d)}	5000 ^{j)}	2500 ^{j)}
Human exposure after a single 16 mg/kg dose of sugammadex ^{l)}		-	160	200	18 ^{m)}	18 ^{m)}
Mature rat-to-human safety margin for effect on bone ⁿ⁾		-	(6.6)	(30)	(17.5)	-
Juvenile rat-to-human safety margin for effects on bone and teeth ^{o)}		-	(2.6)	(2.9)	(8.3)	(12.2)

-: No findings or not applicable

※AUC_{0-∞} and C_{max} (or C₀) values are conservative estimates based on dose-normalized values of pharmacokinetic parameters of unchanged sugammadex in plasma obtained from each study. Safety margins in parentheses.

a) 4.2.3.7.7.1, b) 4.2.3.2.4, c) 4.2.3.5.4.1, 4.2.3.5.4.2, d) 4.2.3.5.4.4,

e) Mean value following single or 4-week repeated intravenous administration of 500 mg/kg of sugammadex in mature rats (4.2.3.2.3) (AUC refers to AUC_{0-3h})

f) AUC and C_{max} following single or 2- to 4-week repeated subcutaneous administration in rats at 1 to 5 weeks of age (4.2.3.5.4.3, 4.2.3.5.4.4)

g) Estimated from the distribution of radioactivity per gram of bone following a single dose of 400 mg/kg of ¹⁴C-sugammadex in mature rats (4.2.2.3.5), i.e. 250 µg/g (sugammadex 500 mg/kg /400 mg/kg × 250 = 313 µg/g)

h) Distribution of radioactivity per gram of bone following 4-week repeated intravenous administration of 30 mg/kg of ¹⁴C-sugammadex in young adult rats (4.2.2.3.5), 2500 to 5000 µg/g

i) Distributions of radioactivity per gram of bone and of teeth following a single intravenous dose of 30 mg/kg of ¹⁴C-sugammadex in juvenile rats (4.2.2.3.5) (when 30 to 400 mg/kg of ¹⁴C-sugammadex was administered to mature rats in this study, the distributions of radioactivity in bone and teeth were highest at 30 mg/kg)

j) Distributions of radioactivity per gram of bone and of teeth following 4-week repeated intravenous administration of 30 mg/kg of ¹⁴C-sugammadex in young adult rats (4.2.2.3.5) (as the distributions of radioactivity per gram of bone and of teeth following a single intravenous dose of 30 mg/kg of ¹⁴C-sugammadex in juvenile rats were about 4.7-fold and 18-fold higher than those in young adult rats, the values in young adult rats were cited)

k) As no effect on teeth was observed in mature rats, exposure was not calculated.

l) A pharmacokinetic study in Japanese and Caucasian healthy adult subjects (5.3.3.3.1, Trial 19.4.102)

m) As the urinary excretion following a single intravenous dose of 4.0 mg/kg of ¹⁴C-sugammadex in foreign healthy adult subjects was ≥85% in a mass balance study (5.3.3.1.5, Trial 19.4.107), assuming that ≤15% of sugammadex is retained in the body, skeletal/teeth exposure in humans was calculated to be about 4.5 µg/g based on the total bone mass in the human body of 10 kg (Brown RP et al, *Toxicol Ind Health*, 13: 407-484, 1997) and then the exposure at 16 mg/kg was calculated to be about 18 µg/g, assuming linearity.

n) AUC and C_{max} following 4-week repeated administration in mature rats were used to determine safety margins and skeletal exposure following a single dose in mature rats was used to determine a safety margin.

o) Sugammadex exposure data after a single dose of 500 mg/kg in juvenile rats were used to determine safety margins.

Furthermore, the applicant explained about bone- or teeth-related adverse events²⁹⁾ reported in clinical trials as follows:

In pooled Japanese and foreign phase II and III trials,³⁰⁾ 4.8% of the subjects treated with sugammadex (83 of 1738 subjects) had bone- or teeth-related adverse events and the main events were arthralgia (0.8%), musculoskeletal pain (1.0%), pain in extremity (1.8%), etc., of which only 1 adverse event (musculoskeletal chest pain) was an event for which a causal

²⁹⁾ Bone- or teeth-related adverse events were identified by the MedDRA High Level Group Terms (HLGTs) and High Level Terms (HLTs), of which the Preferred Terms considered definitely unrelated to bone and teeth (oral infection, skeletal muscle stiffness, pelvic pain) were excluded.

³⁰⁾ Ten phase II trials (5.3.5.1.1, Trial 19.4.201; 5.3.5.1.2, Trial 19.4.202; 5.3.5.1.3, Trial 19.4.203; 5.3.5.1.4, Trial 19.4.204; 5.3.5.1.5, Trial 19.4.205; 5.3.5.1.6, Trial 19.4.206; 5.3.5.1.7, Trial 19.4.207; 5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209; 5.3.5.1.10, Trial 19.4.210) and 11 phase III trials (5.3.5.1.11, Trial 19.4.312; 5.3.5.1.12, Trial 19.4.306; 5.3.5.1.13, Trial 19.4.301; 5.3.5.1.14, Trial 19.4.310; 5.3.5.1.15, Trial 19.4.302; 5.3.5.1.16, Trial 19.4.303; 5.3.5.1.17, Trial 19.4.304; 5.3.5.1.18, Trial 19.4.305; 5.3.5.1.19, Trial 19.4.308; 5.3.5.1.20, Trial 19.4.309; 5.3.5.2.1, Trial 19.4.311) were pooled.

relationship to the drug could not be denied. In pooled Japanese and foreign phase II and III trials with a placebo group,³¹⁾ there were no major differences in the incidence of these adverse events between the sugammadex group (3.0% [19 of 630 subjects]) and the placebo group (2.3% [3 of 130 subjects]).

3.(ii).B.(2) Retention of sugammadex in kidneys and bladder and safety

PMDA asked the applicant to explain the safety of sugammadex for the kidneys and bladder as a high level of radioactivity was distributed into the kidneys and bladder, apart from bone and teeth, following a single intravenous dose of ¹⁴C-sugammadex in rats (4.2.2.5.1, 4.2.2.3.4).

The applicant explained as follows:

Vacuoles in renal tubular cells were observed at 600 to 2000 mg/kg of sugammadex in a rat single intravenous dose toxicity study (4.2.3.1.7) and vacuoles in renal tubular cells and foamy cytoplasm in bladder umbrella cells were observed dose-dependently at 120 to 500 mg/kg/day of sugammadex in rat 2- and 4-week repeated intravenous dose toxicity studies (4.2.3.2.3, 4.2.3.2.4), which were not considered toxicological changes because they were not associated with changes in clinical chemistry or urinalysis, including urine N-acetyl- β -glucosaminidase (NAG), or functional impairment. In a dog 4-week repeat-dose toxicity study (4.2.3.2.6), there were no urinary findings. The safety margins relative to human exposure for these effects are as shown in the following table. The safety margins relative to human exposure following a single intravenous dose of 16 mg/kg of sugammadex are at least 6.6. It is known that vacuoles in renal tubular cells that occur following parenteral administration of cyclodextrins are reversible, adaptive changes (Frank DW et al. *Am J Pathol.* 1976;83:367-382, Maunsbach AB et al. *Lab Invest.* 1962;11:421-432.) and these findings are considered adaptive changes due to sugammadex taken up and retained in renal tubular cells. Since rats have a high glomerular filtration rate (67, 6, and 1.7 mL/min/kg in rats, dogs, and humans, respectively, Walton K et al. *Food Chem Toxicol.* 2004;42: 261-274.), these effects are considered attributable to the fact that rats are susceptible to effects on the urinary organs.

³¹⁾ Six phase II trials (5.3.5.1.1, Trial 19.4.201; 5.3.5.1.2, Trial 19.4.202; 5.3.5.1.5, Trial 19.4.205; 5.3.5.1.6, Trial 19.4.206; 5.3.5.1.7, Trial 19.4.207; 5.3.5.1.8, Trial 19.4.208) and 2 phase III trials (5.3.5.1.12, Trial 19.4.306; 5.3.5.1.20, Trial 19.4.309) were pooled.

Table. NOAELs of sugammadex for effects on kidneys and bladder and safety margins relative to human exposure

		NOAEL (mg/kg)	AUC _{0-∞} (µg·h/mL)	Safety margin relative to human single-dose exposure Sugammadex 16 mg/kg
Effects on rat renal tubular cells/bladder umbrella cells	Single dose	2000 ^{a)}	4200 ^{d)}	22.2
Effects on rat renal tubular cells/bladder umbrella cells	2- and 4-week repeated administration	500 ^{b)}	1050 ^{e)}	6.6
Effects on dog renal tubular cells/bladder umbrella cells	4-week repeated administration	250 ^{c)}	1085 ^{f)}	6.8

※AUC_{0-∞} is a pharmacokinetic parameter of unchanged sugammadex in plasma

a) 4.2.3.1.7, b) 4.2.3.2.3, 4.2.3.2.4, c) 4.2.3.2.6

d) Value calculated by multiplying the dose-normalized AUC_{0-3h} following single and 4-week repeated intravenous administration of 30 to 500 mg/kg of sugammadex (4.2.3.2.3) (NAUC, 2.1 (µg·h/mL)/(mg/kg)) by the dose (AUC_{0-3h}) (AUC_{0-∞} following a single intravenous dose of 2000 mg/kg of sugammadex in rats [4.2.2.2.1] was 4140 µg·h/mL)

e) 4.2.3.2.3, AUC_{0-3h}

f) Value calculated by multiplying the dose-normalized AUC_{0-∞} following single and 3-week repeated intravenous administration of 25 to 250 mg/kg of sugammadex (4.2.2.2.2) (NAUC, 4.34 (µg·h/mL)/(mg/kg)) by the dose

The applicant also explained about adverse events classified as renal and urinary disorders³²⁾ reported in clinical trials as follows:

In pooled Japanese and foreign phase II and III trials,³⁰⁾ 7.0% of subjects treated with sugammadex (122 of 1738 subjects) had adverse events classified as renal and urinary disorders. In pooled Japanese and foreign phase II and III trials with a placebo group, there were no major differences in the incidence between the sugammadex group (6.0% [38 of 630 subjects]) and the placebo group (4.6% [6 of 130 subjects]). Urinary biomarkers, urine β2-microglobulin, NAG, and microalbumin rose above the threshold in 14.7% (55 of 375 subjects), 9.4% (35 of 373 subjects), and 20.7% (61 of 295 subjects), respectively, of the sugammadex group, which were not much different from 13.1% (13 of 99 subjects), 15.2% (15 of 99 subjects), and 25.0% (20 of 80 subjects), respectively, of the placebo group, and there were also no dose-dependent changes. Therefore, sugammadex is unlikely to affect the kidneys.

Taking into account that there were no adverse events related to the effects of sugammadex on bone, teeth, or kidneys in clinical trials and sugammadex is administered as a single dose, PMDA considers that the retention of sugammadex in these tissues is unlikely to become a clinically relevant problem.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Sugammadex is expected to be used as a single dose in a clinical setting. There have been no reports suggesting the carcinogenic potential of β-cyclodextrin (Toyoda K et al. *Food Chem Toxicol.* 1997;35: 331-336, Waner T et al. *Arch Toxicol.* 1995;69: 631-639.). Sugammadex is not genotoxic and there has also been no evidence of preneoplastic lesions in repeat-dose toxicity

³²⁾ Adverse events identified by the MedDRA System Organ Class (SOC): “Renal and urinary disorders”

studies. Therefore, no carcinogenicity studies with sugammadex have been performed. Doses of sugammadex are expressed as the free acid and as the contents of related substances varied from batch to batch, the batch number used in each study is indicated.

3.(iii).A.(1) Single-dose toxicity

Sugammadex (2000 mg/kg, Batch U) was intravenously administered in two divided doses separated by 1 hour to male and female mice (6 males and 6 females per group). No death occurred and 1 male exhibited transient decreased activity, ptosis, and decreased grooming, which were considered of little toxicological significance. The approximate lethal dose was determined to be >2000 mg/kg for both males and females and the NOAEL was determined to be 2000 mg/kg (4.2.3.1.2).

Single intravenous doses of sugammadex (100 and 250 mg/kg, Batch T) were administered to male and female rats (12 males and 12 females per group). No death occurred and males and females receiving 250 mg/kg exhibited increased epithelial cells in urine, which resolved at 2 weeks after drug withdrawal, and there were no associated changes in urinalysis or clinical chemistry. Thus, the approximate lethal dose was determined to be >250 mg/kg and the NOAEL was determined to be 250 mg/kg (4.2.3.1.5).

Single intravenous doses of sugammadex (100 and 250 mg/kg, Batch V) were administered to male and female rats (12 males and 12 females per group). Since no death occurred and there were no abnormalities in clinical observations, body weight, hematology, clinical chemistry, organ weights, necropsy, or histopathological examination, the approximate lethal dose was determined to be >250 mg/kg and the NOAEL was determined to be 250 mg/kg (4.2.3.1.6).

Single intravenous doses of sugammadex (200, 600, 2000 mg/kg,³³⁾ Batch AE) were administered to male and female rats (12 males and 12 females per group). No death occurred and clinical chemistry findings included slight increases in blood inorganic phosphate in females at 600 mg/kg and males and females at 2000 mg/kg and histopathological findings included vacuolation of the tubular epithelium in males and females at ≥ 600 mg/kg and foamy alveolar macrophages in males and females at 2000 mg/kg, but there were no associated changes in clinical chemistry or urinalysis. Thus, the approximate lethal dose was determined to be >2000 mg/kg and the NOAEL was determined to be 2000 mg/kg (4.2.3.1.7).

³³⁾The highest dose was chosen in view of the slight hypertonicity of the drug solution (100 mg/mL) and according to the total administration volumes recommended by the European Federation of Pharmaceutical Industries and Associations (Diehl KH *et al. J Appl Toxicol.* 2001;21(1): 15-23.) (20 mL/kg for single dosing in rats, 2.5 mL/kg for multiple intravenous dosing in dogs).

Rocuronium (0 and 1.08 mg/kg) and sugammadex (2.76 and 27.6 mg/kg, Batch L) were intravenously administered in three divided doses separated by 30 minutes (sugammadex was administered at 2 minutes after the administration of rocuronium) to male and female dogs under propofol/isoflurane anesthesia (4 males and 4 females per group). No death occurred and there were no abnormalities in clinical observations, body weight, hematology, clinical chemistry, organ weights, necropsy, histopathological examination, blood gas analysis, ECG, blood pressure, or heart rate. Thus, the approximate lethal dose of sugammadex when combined with rocuronium was determined to be >27.6 mg/kg and the NOAEL was determined to be 27.6 mg/kg (4.2.3.1.9).

Rocuronium (0, 1.08, 10.8, and 54 or 108³⁴⁾ mg/kg) and sugammadex (0, 2.76, 39, and 195 or 390³⁴⁾ mg/kg, Batch AM) were intravenously administered in three divided doses separated by 30 minutes (sugammadex was administered at 2 minutes after the administration of rocuronium) to male and female dogs under propofol/isoflurane anesthesia (4-5 males and 4-5 females per group).³⁵⁾ One male in the 195 mg/kg group was sacrificed because reversal of neuromuscular blockade was not achieved, but none of the dogs died. One female in the 195 mg/kg group exhibited increased blood urea nitrogen, increased creatinine, and increased kidney weight and the ECGs showed transient decreases in blood pressure, decreased heart rate, and QTc interval prolongation in the 195 mg/kg group. Thus, the approximate lethal dose of sugammadex when combined with rocuronium was determined to be >195 mg/kg and the NOAEL was determined to be 39 mg/kg (4.2.3.1.10).

Rocuronium (0 and 1.5 mg/kg) and sugammadex (2.76 and 27.6 mg/kg, Batch L) were intravenously administered in three divided doses separated by 30 minutes to male and female cats under propofol/isoflurane anesthesia (4 males and 4 females per group). No death occurred and there were no abnormalities in clinical observations, body weight, hematology, clinical chemistry, organ weights, necropsy, histopathological examination, blood gas analysis, ECG, blood pressure, or heart rate. Thus, the approximate lethal dose of sugammadex when combined with rocuronium was determined to be >27.6 mg/kg and the NOAEL was determined to be 27.6 mg/kg (4.2.3.1.11).

³⁴⁾ As the high dose group, 1 male intravenously received 108 mg/kg of rocuronium and 390 mg/kg of sugammadex (in three divided doses), but reversal of neuromuscular blockade was not achieved. Thus, the doses of rocuronium and sugammadex were reduced to 54 mg/kg and 195 mg/kg, respectively, thereafter. This animal was sacrificed because reversal of neuromuscular blockade was not achieved, and was excluded from evaluations other than mortality.

³⁵⁾ If reversal of neuromuscular blockade was not achieved, the same divided dose of sugammadex was repeated. One female received 1 additional dose of 13 mg/kg and 2 males and 3 females received 1 additional dose of 65 mg/kg, 1 male received 2 additional doses of 65 mg/kg, 1 female received 3 additional doses of 65 mg/kg, and 1 male received 4 additional doses of 65 mg/kg.

3.(iii).A.(2) Repeat-dose toxicity

Following 4-week repeated intravenous administration of sugammadex (30, 120, 500 mg/kg/day, Batch U) in male and female rats (10-20 males and 10-20 females per group), no death occurred and 1 male in the 500 mg/kg/day group exhibited transient staggering gait of the hindlimbs immediately after dosing and reduced body weight gain associated with a slight decrease in food consumption and decreased water consumption were observed in the 500 mg/kg/day group, but there were no abnormalities in the relative body weight. Histopathological examination revealed vacuoles in renal tubular cells and bladder epithelium hyperplasia in males and females at ≥ 120 mg/kg/day and increased alveolar macrophages in males and females at 500 mg/kg/day, but there were no associated changes in clinical chemistry or urinalysis. All findings except for bladder epithelium hyperplasia resolved or tended to resolve after a 3-week recovery period. Based on the above, the NOAEL was determined to be 500 mg/kg/day (4.2.3.2.3).

Following 4-week repeated intravenous administration of sugammadex (30, 120, 500 mg/kg/day, Batch AE) in male and female rats (10-20 males and 10-20 females per group), although no death occurred, reduced body weight gain in males at 500 mg/kg/day and reduced food consumption in females at 500 mg/kg/day were observed. Hematological examination showed slight increases in reticulocyte count in females at all dose levels and histopathological examination revealed foamy cytoplasm in umbrella cells in males and females at ≥ 120 mg/kg/day, vacuoles in renal tubular cells in males at 120 mg/kg/day and males and females at 500 mg/kg/day, and foamy alveolar macrophages at 500 mg/kg/day, but there were no associated changes in clinical chemistry or urinalysis. All findings except for foamy cytoplasm in umbrella cells resolved or tended to resolve after a 8-week recovery period. Based on the above, the NOAEL was determined to be 500 mg/kg/day (4.2.3.2.4).

Following 4-week repeated intravenous administration of sugammadex (25, 80, 250 mg/kg/day,³³) Batch U) in male and female dogs (4-6 males and 4-6 females per group), no death occurred and there were no abnormalities in clinical observations, body weight, ECG, hematology, clinical chemistry, blood coagulation test, urinalysis, organ weights, necropsy, or histopathological examination. Thus, the NOAEL was determined to be 250 mg/kg/day (4.2.3.2.6).

3.(iii).A.(3) Genotoxicity (4.2.3.3.1.1-4.2.3.3.1.5, 4.2.3.3.1.8-4.2.3.3.1.11, 4.2.3.3.2.1, 4.2.3.3.2.2)

Bacterial reverse mutation tests (Batches L, T, V, AE, AM), chromosomal aberration tests in human peripheral blood lymphocytes (Batches L, T, V, AE), and mouse/rat micronucleus tests

(Batches S, AE) were performed. As a result, sugammadex was determined to be negative for genotoxicity in all of these tests.

3.(iii).A.(4) Reproductive and developmental toxicity

3.(iii).A.(4).1) Rat study of fertility and early embryonic development to implantation (4.2.3.5.1.1)

Sugammadex (20, 100, 500 mg/kg/day, Batch U) was intravenously administered to male and female rats (22 males and 22 females per group) from 4 weeks prior to, and throughout mating for males and from 2 weeks prior to mating until gestation day 5 for females. None of the parent animals died. While reduced body weight gain, piloerection, and hunched position during gestation in females at 500 mg/kg/day and very slight decreases in food consumption in males at ≥ 100 mg/kg/day were observed, there were no effects on fertility or early embryonic development. Based on the above, the NOAELs for paternal and maternal general toxicity were determined to be 500 mg/kg/day and 100 mg/kg/day, respectively, and the NOAEL for parental reproductive toxicity and early embryonic development was determined to be 500 mg/kg/day for both males and females.

3.(iii).A.(4).2) Embryo-fetal development studies in rats and rabbits

Sugammadex (20, 100, 500 mg/kg/day, Batch U) was intravenously administered to pregnant rats (n = 19-22 per group) from gestation day 6 to gestation day 17. None of the maternal animals died. While transient reductions in body weight gain and reductions in food consumption were observed at ≥ 100 mg/kg/day, there were no effects on embryo-fetal development. Based on the above, the NOAELs for maternal animals and for embryo-fetal development were both determined to be 500 mg/kg/day (4.2.3.5.2.1).

Sugammadex (20, 65, 200 mg/kg/day, Batch U) was intravenously administered to pregnant rabbits (n = 19-20 per group) from gestation day 6 to gestation day 18. While none of the maternal animals died, reduced body weight gain and decreased food consumption were noted on gestation days 6 to 9 in the 200 mg/kg/day group. Although fetal weights were reduced dose-dependently, the applicant discussed that fetal weights were reduced due to increased numbers of implantation sites and fetuses per dam and no teratogenic effects were observed. Based on the above, the NOAELs for maternal general toxicity and for embryo-fetal development were determined to be 65 mg/kg/day and 200 mg/kg/day, respectively (4.2.3.5.2.2).

3.(iii).A.(4).3) Rat studies for effects on pre- and postnatal development, including maternal function

Sugammadex (30, 120, 500 mg/kg/day, Batch W) was intravenously administered to pregnant rats (n = 20-22 per group) from gestation day 6 through lactation day 21. No death or drug-related changes in clinical observations were observed in the maternal animals. Although post-implantation loss was increased at 120 mg/kg/day and postnatal mortality to day 4 was increased at ≥ 120 mg/kg/day, one dam in the 500 mg/kg/day group was found to cannibalize 3 pups at the first observation after delivery and the applicant discussed that based on maternal body weights before and after delivery, other dams also may have cannibalized pups. Histopathological examination of the cannibalized pups revealed no abnormalities and there were no effects on the development or reproductive function of offspring (4.2.3.5.3.1).

Two additional studies were conducted to investigate the relationship between sugammadex and pup deaths. Sugammadex (500 mg/kg/day, Batch AE) was intravenously administered to pregnant rats (n = 5-21 per group) during 6 different gestation/lactation periods (from gestation day 6 to lactation day 4, from gestation day 6 to gestation day 20, from gestation day 6 to gestation day 10, from gestation day 11 to gestation day 15, from gestation day 16 to gestation day 20, from gestation day 21 to lactation day 4). In the rats treated with sugammadex from gestation day 6 to gestation day 20, there were no abnormalities in post-implantation loss, the number of live fetuses, or the number of dead fetuses at caesarean section. In the rats treated with sugammadex from gestation day 16 to gestation day 20, postnatal survival to 24 hours was decreased due to cannibalism. Histopathological examinations of the cannibalized pups, dead pups, and stillborn pups revealed no developmental abnormalities, e.g. malformations that would cause death or cannibalism (4.2.3.5.3.2). When sugammadex (500 mg/kg/day, Batch AE) was intravenously administered to pregnant rats (n = 18-22) from gestation day 6 to gestation day 21 and their pups with intrauterine exposure to sugammadex were fostered to untreated surrogate dams, cannibalism of pups occurred. Meanwhile, when sugammadex was applied to the skin of pups born naturally to untreated dams, postnatal survival was not decreased. Therefore, the applicant discussed that an alteration in the taste or smell of pups due to intrauterine exposure to sugammadex induces cannibalism, resulting in increased pup mortality (4.2.3.5.3.3).

Based on the above, the observed pup deaths are of no clinical significance and the NOAELs for maternal general toxicity and for offspring were both determined to be 500 mg/kg/day.

3.(iii).A.(5) Juvenile animal studies

(a) Single-dose toxicity studies in juvenile rats

Following single subcutaneous (for rats at 7 and 14 days of age) or intravenous (for rats at 21 days of age) doses of sugammadex (120 and 500 mg/kg, Batch AM) in male and female rats at 7, 14, and 21 days of age (16 males and 16 females per group), 1 female at 21 days of age in the 120 mg/kg group was sacrificed due to poor general condition at 1 day post-dose. Transient reduced body weight gain was noted at 5 days post-dose in females at 21 days of age in the 500 mg/kg group. Increased liver weights were observed at 1 day post-dose in males at 7 days of age in the 500 mg/kg group and males at 14 days of age in the 500 mg/kg group and at 1 day and 14 days post-dose in females at 14 days of age in the 500 mg/kg group. Histopathological examination revealed vacuoles in renal tubular cells at 1 day post-dose in males and females at 7 and 14 days of age in the 500 mg/kg group and decay in the enamel surface of the incisors and deposition of amorphous substances at 14 days post-dose in 1 female at 21 days of age in the 500 mg/kg group. These findings are considered of little toxicological significance and the NOAEL was determined to be 500 mg/kg at all three ages (4.2.3.5.4.1).

Single subcutaneous doses of sugammadex (30, 120, 500 mg/kg, Batch AM) were administered to male and female rats at 7 days of age (23-24 males and 23-24 females per group) to investigate the effects on the incisors. Although 1 male and 1 female in the 30 mg/kg group were sacrificed due to poor general condition or severe ocular inflammation, none of the rats died and there were no changes in clinical observations, body weight, or teeth. Thus, the NOAEL was determined to be 500 mg/kg (4.2.3.5.4.2).

(b) Four-week repeat-dose toxicity study in juvenile rats (4.2.3.5.4.4)

Following 4-week repeated administration of sugammadex (30, 120, 500 mg/kg/day, Batch AM) (2-week subcutaneous administration followed by 2-week intravenous administration) in male and female rats at 7 days of age (22 males and 22 females per group), injection procedure-related death occurred in 1 male in the 30 mg/kg/day group and 1 male and 1 female in the 120 mg/kg/day group, and 1 male in the 500 mg/kg/day group was sacrificed due to poor general condition during the recovery period. The one sacrificed animal had darkening and enlargement of the adrenal gland and abnormal left ureter and kidney. Among the surviving animals, males at ≥ 120 mg/kg/day exhibited slight reductions in body weight gain after the 2nd week of the recovery period. Clinical chemistry findings included increases in blood potassium in males at ≥ 30 mg/kg/day and increases in blood glucose in females at ≥ 120 mg/kg/day, which resolved during an 8-week recovery period. Histopathological findings included vacuoles in renal tubular cells and vacuoles in bladder umbrella cells in males and females at ≥ 120

mg/kg/day and foamy alveolar macrophages in males and females at 500 mg/kg/day. Bone examinations, including three-dimensional micro-CT analysis, revealed retardation of femur growth in males and females at ≥ 120 mg/kg/day and retardation of ulnar growth in males at 500 mg/kg/day. Findings on teeth included decay in the enamel surface of the incisors and deposition of amorphous substances in males and females at ≥ 120 mg/kg/day and incisor discoloration (marbly/patchy/striped pattern), malocclusion, overgrowth of the incisors, and deposition of amorphous substances in the molars in males and females at 500 mg/kg/day, and the incisor discoloration resolved at the 5th week of the recovery period. Based on the above, the NOAEL was determined to be 30 mg/kg/day.

3.(iii).A.(6) Local tolerance (4.2.3.6.1)

Following single intravenous, intramuscular, subcutaneous, or intraarterial administration of 0.5 mL of Sugammadex (100 mg/mL) or single perivenous administration of 0.2 mL of Sugammadex (100 mg/mL) in female rabbits (n = 6 per group), no acute or delayed local reactions were observed.

3.(iii).A.(7) Blood compatibility study (4.2.3.6.2)

The human blood compatibility of sugammadex (0-3.26 mM) was evaluated *in vitro* in the presence or absence of an equimolar concentration of rocuronium. As a result, no hemolysis or red blood cell fragility was noted.

3.(iii).A.(8) Other toxicity studies

3.(iii).A.(8).1 Immunotoxicity

Two-week repeated intravenous administration of sugammadex (30, 120, 500 mg/kg/day) had no effect on the primary antibody response to sheep red blood cells (T-cell dependent antigen) in male and female rats (8 males and 8 females per group), as measured by the plaque-forming cell assay (4.2.3.7.2.3).

Sugammadex (0.3, 1.2, 5 mg) was administered subcutaneously into the footpad of female mice (n = 8 per group) in the popliteal lymph node assay. As a result, an increase in the ^3H -thymidine incorporation without an increase in popliteal lymph node weight was observed at 5 mg of sugammadex, but the degree of the increase was lower than that induced by a commonly known sensitizer (HgCl_2) (4.2.3.7.2.1).

Sugammadex (2.4, 6, 12 mg) was applied to female mice (n = 5 per group) for 3 days in the local lymph node assay. As a result, sugammadex showed no sensitizing effect (4.2.3.7.2.2).

3.(iii).A.(8).2 Effects on bone and teeth

Following a single intravenous dose of sugammadex (2000 mg/kg) in male and female rats (16 males and 16 females per group), micro-CT analysis and bone strength assessments showed increased trabecular separation, reduced trabecular number, and decreased compressive strength, suggesting bone resorption in the femur. According to clinical chemistry examination and urinalysis for biochemical bone turnover markers, type I collagen C-terminal telopeptide was increased, but urinary deoxypyridinoline was decreased and there were no changes in blood osteocalcin or blood alkaline phosphatase. The findings suggestive of bone resorption in the femur were most notable at 21 days post-dose in females, which were all slight changes and reversed or excessively reversed at 42 days post-dose. Following single intravenous doses of sugammadex (30, 120, 500 mg/kg) in male and female rats (24 males and 24 females per group), no death occurred and there were no changes in clinical observations, body weight, urine volume, bone mineral density of femoral cortex, or trabecular bone mineral density, or micro-CT analysis. Based on the above, the NOAEL was determined to be 500 mg/kg/day (4.2.3.7.7.1, 4.2.3.7.7.2).

Following single intravenous doses of sugammadex (30, 120, 500 mg/kg) in female rats (n = 6 per group), there was a dose-dependent, transient PTH surge at 3 to 10 minutes post-dose and blood calcium was increased within 30 minutes post-dose and the urinary phosphorus/creatinine ratio was increased within 24 hours post-dose at 500 mg/kg. These changes were slight and the applicant has been discussed that a PTH surge is associated with a decrease in blood calcium (4.2.3.7.7.3).

Following single intravenous doses of sugammadex (25, 80, 250 mg/kg) in male and female dogs (3 males and 3 females per group), there was a transient, slight surge in blood PTH up to 10 to 15 minutes post-dose in males and females at ≥ 80 mg/kg (4.2.2.2.2).

3.(iii).A.(9) Toxicity studies with related substances or intentionally degraded sugammadex

A single intravenous dose of non-degraded sugammadex (2000 mg/kg) or intentionally degraded sugammadex³⁶⁾ (200, 600, 2000 mg/kg) was given to male and female rats (11-13 males and 11-13 females per group). As a result, 1 female treated with non-degraded sugammadex and 1 male treated with 2000 mg/kg of intentionally degraded sugammadex died due to errors in blood sampling, and 1 male treated with 2000 mg/kg of intentionally degraded sugammadex died due to lung compression when held in a restrainer. Urinalysis showed urinary

³⁶⁾ A mixture of the drug substance batches U, W, and Z was used as non-degraded sugammadex (total level of organic impurities, ██████%) and non-degraded sugammadex was autoclaved at 121°C for 30 minutes and then stored at 60°C for 2 months and at 25°C for 7 weeks, which was used as intentionally degraded sugammadex (total level of organic impurities, 14.3%).

occult blood (urinary hemoglobin) at 1 day post-dose in males and females in the non-degraded sugammadex group and in the intentionally degraded sugammadex 2000 mg/kg group. Histopathological examination revealed vacuolation of the tubular epithelium and foamy alveolar macrophages in males and females in the non-degraded sugammadex group and in the intentionally degraded sugammadex ≥ 600 mg/kg groups. These findings resolved during a 2-week recovery period and there were no associated findings suggestive of functional impairment. Therefore, the approximate lethal dose was determined to be >2000 mg/kg for both non-degraded and intentionally degraded sugammadex and the NOAEL was determined to be 2000 mg/kg (4.2.3.1.8).

Following 2-week repeated intravenous administration of intentionally degraded sugammadex ³⁶⁾ (46, 92, 184 mg/kg/day) in male and female rats (8 males and 8 females per group), no death occurred and very slight reductions in body weight gain and reduced food consumption were observed in males at 184 mg/kg/day. Histopathological findings included vacuoles in renal tubular cells in males and females at ≥ 46 mg/kg/day, foamy cytoplasm in bladder umbrella cells in males at 46 mg/kg/day and males and females at 92 mg/kg/day, and foamy alveolar macrophages in males and females at 184 mg/kg/day, whereas there were no abnormalities in hematology, blood coagulation test, clinical chemistry, urinalysis (including NAG), organ weights, or necropsy. Therefore, the NOAEL of intentionally degraded sugammadex was determined to be 184 mg/kg/day (4.2.3.2.2).

Genotoxicity studies with Related Substance Org 48302 (a bacterial reverse mutation test, a chromosomal aberration test in human peripheral blood lymphocytes, a rat micronucleus test) and genotoxicity studies with Related Substance Org 48301 (the molecule contains bromine), the octabromo derivative of γ -cyclodextrin, Batch AJ (Org 25969 content was artificially reduced to one-seventh to one-eighth by chromatography), or intentionally degraded sugammadex ³⁶⁾ (bacterial reverse mutation tests and chromosomal aberration tests in human peripheral blood lymphocytes) all produced negative results (4.2.3.3.1.6, 4.2.3.3.1.7, 4.2.3.3.1.12, 4.2.3.3.1.13, 4.2.3.3.2.2, 4.2.3.7.6.2-4.2.3.7.6.8).

The human blood compatibility of Related Substance Org48302 (0-3.57 mM) was evaluated *in vitro* in the presence or absence of an equimolar concentration of rocuronium. As a result, no hemolysis or red blood cell fragility was noted (4.2.3.7.6.1).

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Safety of related substances of sugammadex

PMDA asked the applicant to explain the safety of related substances present in the drug substance and drug product at a level greater than the qualification threshold in humans.

The applicant explained as follows:

Based on the results of general toxicity studies with different drug substance batches, the safety margins of related substances present in the drug substance and drug product at a level greater than the qualification threshold were calculated as shown in the following table. The safety margins of all related substances except for Related Substance M-1 are >1. Related Substance M-1 is a compound that is co-eluted with Related Substance M-2¹⁾ (Related Substance M) and the NOAELs used for calculating the safety margins were all the maximum doses used in the toxicity studies and Related Substance M-1 has not been detected in Batch Z and subsequent batches manufactured after the action limit for [REDACTED], which is related with the level of Related Substance M-1 formed, was changed to ≤ [REDACTED]%. Therefore, there should be no safety problems. Furthermore, since the safety margins in the following table are estimates assuming that toxicity effects are attributed to individual related substances only, the actual safety margins would be higher.

Table. Safety margins of related substances present in the drug substance and drug product at a level greater than the qualification threshold, relative to the human dose (a single intravenous dose of 16 mg/kg of sugammadex)

Related substance	Specification limit ^{a)}	Maximum clinical dose ^{b)}	Toxicity study ^{c)} Batch identity	NOAEL	Maximum permissible level of related substance ^{d)}	Safety margin
Org48302	Drug product: ≤ [REDACTED]%	[REDACTED] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[REDACTED] mg	1.3
Related Substance A	Drug substance: ≤ [REDACTED]%	[REDACTED] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[REDACTED] mg	83
Org48301	Drug substance: ≤ [REDACTED]%	[REDACTED] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[REDACTED] mg	46
Related Substance B	Drug substance: ≤ [REDACTED]%	[REDACTED] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[REDACTED] mg	12
Related Substance C	Drug product: ≤ [REDACTED]%	[REDACTED] mg	Rat single-dose toxicity study (4.2.3.1.8), intentionally degraded sugammadex	2000 mg/kg	[REDACTED] mg	7.1
Related Substance D	Drug product: ≤ [REDACTED]%	[REDACTED] mg	Rat single-dose toxicity study (4.2.3.1.7), AE	2000 mg/kg	[REDACTED] mg	19
Related Substance E	Drug product: ≤ [REDACTED]%	[REDACTED] mg	Rat single-dose toxicity study (4.2.3.1.8), intentionally degraded	2000 mg/kg	[REDACTED] mg	26

Related substance	Specification limit ^{a)}	Maximum clinical dose ^{b)}	Toxicity study ^{c)} Batch identity	NOAEL	Maximum permissible level of related substance ^{d)}	Safety margin
			sugammadex			
Related Substance F	Drug substance: ≤ [redacted]%	[redacted] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[redacted] mg	16
Related Substance G	Drug product: ≤ [redacted]%	[redacted] mg	Rat single-dose toxicity study (4.2.3.1.8), intentionally degraded sugammadex	2000 mg/kg	[redacted] mg	24
Related Substance H	Drug substance: ≤ [redacted]%	[redacted] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[redacted] mg	10
Related Substance I	Drug product: ≤ [redacted]%	[redacted] mg	Rat single-dose toxicity study (4.2.3.1.8), intentionally degraded sugammadex	2000 mg/kg	[redacted] mg	24
Related Substance J	Drug substance: ≤ [redacted]%	[redacted] mg	Rat single-dose toxicity study (4.2.3.1.7), AE	2000 mg/kg	[redacted] mg	16
Related Substance K Related Substance K-1 ^{e)}	Drug substance: ≤ [redacted]%	[redacted] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[redacted] mg	6.0
Related Substance K Related Substance K-2 ^{e)}	Drug product: ≤ [redacted]%	[redacted] mg	Rat single-dose toxicity study (4.2.3.1.8), intentionally degraded sugammadex	2000 mg/kg	[redacted] mg	13
Related Substance L Related Substance L-1 ^{e)}	Drug substance: ≤ [redacted]%	[redacted] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[redacted] mg	2.9
Related Substance L Related Substance L-2 ^{e)}	Drug substance: ≤ [redacted]%	[redacted] mg	Juvenile rat single-dose toxicity study (4.2.3.5.4.1), AM	500 mg/kg	[redacted] mg	4.4
Related Substance M Related Substance M-1 Related Substance M-2	Drug substance: ≤ [redacted]%	[redacted] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[redacted] mg	2.8
Related Substance M Related Substance M-1 ^{e)}	Drug substance: ≤ [redacted]%	[redacted] mg	Dog 2-week repeat-dose toxicity study (4.2.3.2.5), L	27.6 mg/kg	[redacted] mg	0.65
Related Substance M Related Substance M-2 ^{e)}	Drug substance: ≤ [redacted]%	[redacted] mg	Juvenile rat single-dose toxicity study (4.2.3.5.4.1), AM	500 mg/kg	[redacted] mg	3.5
Related Substance N	Drug substance: ≤ [redacted]%	[redacted] mg	Dog 4-week repeat-dose toxicity study (4.2.3.2.6), U	250 mg/kg	[redacted] mg	2.9

- a) If the specification limit is different between the drug substance and drug product, the higher one only is listed.
- b) Maximum clinical dose = Maximum recommended human dose (16 mg/kg) × the specification limit for related substance (%) × human body weight (60 kg)
- c) Based on related substance content of the drug substance batches used for studies and the NOAELs, a study with the highest exposure was selected (it was explained that the effects on bone and teeth observed in a juvenile rat 4-week repeat-dose toxicity study were due to accumulation of sugammadex and would not become a problem following a single dose of sugammadex, and this study was excluded from selection).
- d) Maximum permissible level of related substance = NOAEL (mg/kg) × related substance content of the drug substance batch used for study (%) × human body weight (60 kg) divided by the correction factor for species difference in exposure (the correction factor was calculated to be 5 for rats and 2.5 for dogs, based on the ratio of the dose-normalized AUC_{0-∞} [NAUC] following 4-week repeated intravenous administration to rats [4.2.3.2.3] or 3-week repeated intravenous administration to dogs [4.2.2.2.2] to the NAUC in a pharmacokinetic study in Japanese and Caucasian healthy adult subjects [5.3.3.3.1, Trial 19.4.102])
- e) Although two different compounds are co-eluted, when these were separated and identified by [redacted], the other compound was not detected for a certain batch. The data from this batch were used for calculation.
- f) Although a specification limit of ≤ [redacted]% has been set as [redacted] for the drug product, as this related substance is a by-product in the manufacturing process and degradation does not occur in the drug product, the safety margin over the specification limit for the drug substance was calculated.

PMDA accepted the above and concluded that there are no particular problems with the safety of related substances.

3.(iii).B.(2) Safety concerns about the hemolytic potential of sugammadex

Since γ -cyclodextrin is known to induce hemolysis, PMDA asked the applicant to explain the safety of sugammadex in terms of its hemolytic potential.

The applicant explained as follows:

The *in vitro* hemolytic effects of α -, β -, and γ -cyclodextrins at high concentrations (≥ 6 , ≥ 3 , and ≥ 16 mM, respectively, Irie Y et al, *J Pharm Dyn*, 1982;5:741-744) have been reported. Also with sugammadex, urinary occult blood (urinary hemoglobin) was observed in a rat single intravenous dose toxicity study with non-degraded and intentionally degraded sugammadex (4.2.3.1.8), but there were no effects on red blood cell count, hematocrit value, or hemoglobin concentration. In a rat 4-week repeated intravenous dose toxicity study (4.2.3.2.4) and a juvenile rat single intravenous dose toxicity study (4.2.3.5.4.1), decreases in red blood cell count, decreases in hematocrit value, decreases in hemoglobin concentration, and increases in reticulocyte count were observed, but there were no direct findings suggestive of hemolysis. These findings were not observed in other toxicity studies and were poorly reproducible. In *in vitro* blood compatibility studies with sugammadex (3.26 mM) and Related Substance Org48302 (3.57 mM) (4.2.3.6.2, 4.2.3.7.6.1), no hemolysis or red blood cell osmotic fragility was noted and the doses used in these studies were ≥ 30 times the maximum plasma concentration (about 0.1 mM) in humans following a single intravenous dose of 16 mg/kg.

The applicant also explained about adverse events classified as hemolytic disorders³⁷⁾ reported in clinical trials as follows:

In pooled Japanese and foreign phase II and III trials,³⁰⁾ 0.3% of subjects (5 of 1738 subjects) had adverse events classified as hemolytic disorders (haptoglobin decreased [4 subjects] and hemolysis [1 subject]), which were all mild in severity. In pooled Japanese and foreign phase II and III trials with a placebo group,³¹⁾ bilirubin was increased above the reference range in 1.3% (5 of 394 subjects) of the sugammadex group and 1.0% (1 of 104 subjects) of the placebo group and haptoglobin was decreased below the reference range in 16.8% (53 of 316 subjects) of the sugammadex group and 14.1% (12 of 85 subjects) of the placebo group, showing no major differences between the two groups, and there were also no dose-dependent changes by sugammadex. Therefore, sugammadex is unlikely to increase the risk of hemolysis in humans.

PMDA accepted the above and concluded that there are no particular problems with the safety of sugammadex in terms of its hemolytic potential.

³⁷⁾ Adverse events were identified by the MedDRA Preferred Terms: hemolysis, hemolytic anaemia, haptoglobin decreased, and intravascular hemolysis.

4. Clinical data

4.(i) Summary of human pharmacokinetic and pharmacodynamic trials

4.(i).A Summary of the submitted data

As the evaluation data, the results from a phase I trial in Japanese and Caucasian healthy adult subjects (5.3.3.3.1, Trial 19.4.102), a phase II trial in Japanese and Caucasian surgical patients (5.3.5.1.8, Trial 19.4.208), phase I trials in foreign healthy adult subjects (5.3.3.1.2, Trial 19.4.101; 5.3.3.1.4, Trial 19.4.106; 5.3.3.1.5 and 5.3.3.1.6, Trial 19.4.107; 5.3.3.1.7, Trial 19.4.108), phase II trials in foreign patients (5.3.5.1.1, Trial 19.4.201; 5.3.5.1.2, Trial 19.4.202; 5.3.5.1.5, Trial 19.4.205; 5.3.5.1.6, Trial 19.4.206; 5.3.5.1.7, Trial 19.4.207; 5.3.5.1.10, Trial 19.4.210), a phase III trial in foreign patients (5.3.5.1.22, Trial 19.4.312), QT/QTc trials (5.3.3.1.3, Trial 19.4.105; 5.3.3.1.8, Trial 19.4.109), and trials in special populations (5.3.5.1.17, Trial 19.4.304; 5.3.5.1.18, Trial 19.4.305; 5.3.5.1.12, Trial 19.4.306) were submitted. As the reference data, the results from a skin prick study (Reference data 5.3.3.1.9, Trial 19.4.110), a study to investigate the effects on hemostasis parameters (Reference data 5.3.5.1.11, Trial 19.4.115), and a study to assess the re-use of neuromuscular blocking agents after sugammadex administration (Reference data 5.3.3.1.10, Trial 19.4.113) were submitted and the results from *in vitro* studies using human biomaterials (4.2.2.3.1, 4.2.2.3.2, 5.3.2.3.1, 5.3.2.3.2, 5.3.2.3.3, Reference data 5.3.2.3.4, Reference data 5.3.2.3.5) were also submitted. Concentrations of unchanged sugammadex and Related Substance Org48302 in biomaterials were determined by LC-MS according to validated procedures (Lower limit of quantification, 0.1-100 µg/mL for sugammadex; 0.2-0.5 µg/mL for Org48302). Since complex-bound and non-complex-bound concentrations can not be determined separately using these analytical methods, pharmacokinetic parameters were calculated from the total sum of complex-bound and non-complex-bound concentrations of unchanged sugammadex, Related Substance Org48302, rocuronium, or vecuronium and are expressed as the mean or the mean ± SD, unless otherwise specified. Doses are expressed as the free acid.

4.(i).A.(1) *In vitro* studies using human biomaterials

4.(i).A.(1).1 Extent of binding to human plasma proteins or erythrocytes

When human plasma was added with ¹⁴C-sugammadex at final concentrations of 0 to 125 µM, sugammadex did not bind to plasma proteins, as determined by an equilibrium dialysis method. When sugammadex (0-12.5 µM) and ³H-rocuronium (0.24-11.1 µM) were added at a sugammadex to rocuronium molar ratio of 0 to 1.1, the extent of binding of ³H-rocuronium to plasma proteins, as determined by an equilibrium dialysis method, decreased with increasing ratio of sugammadex to rocuronium and reached 0% at an almost equimolar ratio of sugammadex to rocuronium (4.2.2.3.1).

When human blood was added with ¹⁴C-sugammadex at final concentrations of 0 to 250 µM, ¹⁴C-sugammadex did not bind to erythrocytes (4.2.2.3.2).

4.(i).A.(1).2) *In vitro* study on the dialysability of sugammadex

When human plasma was added with sugammadex at a final concentration of 100 µg/mL and dialyzed using a low-flux membrane at a plasma flow rate of 200 mL/min and a dialysate (phosphate-bicarbonate buffer) flow rate of 500 mL/min, the clearance was 6.0 mL/min. When human plasma was added with sugammadex (100 µg/mL) and rocuronium (30 µg/mL) at an equimolar ratio and dialyzed using low-flux and high-flux membranes at a plasma flow rate of 200 mL/min and a dialysate flow rate of 500 mL/min, the clearances of sugammadex and rocuronium were 3.9 and 6.3 mL/min, respectively, for the low-flux membrane and 86.3 and 89.0 mL/min, respectively, for the high-flux membrane. Thus, the applicant discussed that sugammadex and rocuronium are efficiently removed from plasma via dialysis using a high-flux membrane (5.3.2.3.3).

4.(i).A.(1).3) Effects on clinical chemistry analysis

Serum, plasma, and whole blood samples collected from 6 foreign healthy adult subjects (3 male and 3 female subjects) were spiked with 100 µg/mL sugammadex, and the possible effects of sugammadex on the results of 72 different clinical chemistry parameters were assessed. As a result, the activated partial thromboplastin time (APTT), prothrombin time (PT), and PT international normalized ratio (PT-INR) were prolonged and the result of the progesterone assay (female subjects only) was lower for samples spiked with sugammadex. When urine samples collected from 2 foreign healthy adult subjects were spiked with 500 µg/mL sugammadex and the possible effects of sugammadex on the results of 13 different clinical chemistry parameters were assessed, none of the parameters were abnormal (outside the reference ranges) for spiked samples (5.3.2.3.1).

Serum, plasma, whole blood, and urine samples from 6 foreign healthy adult subjects (3 male and 3 female subjects) were spiked with sugammadex (90 µg/mL for serum, plasma, and whole blood; 450 µg/mL for urine) or Related Substance Org48302 (10 µg/mL for serum, plasma, and whole blood; 50 µg/mL for urine) and the possible effects of sugammadex or Org48302 on the results of 23 different clinical chemistry parameters were assessed. As a result, the APTT, PT, and PT-INR were prolonged for samples spiked with sugammadex or Org48302, but the differences in the parameters between spiked and un-spiked samples were smaller for Org48302 compared with sugammadex (5.3.2.3.2).

4.(i).A.(1).4) Mechanism of effects on blood coagulation system

When whole blood samples collected from 6 foreign healthy adult subjects (3 male and 3 female subjects) were spiked with 25 to 400 µg/mL of sugammadex, activated clotting time (ACT) was increased dose-dependently (increases of 7%-33%). When human platelet-rich plasma (platelet count, $30 \times 10^4/\mu\text{L}$) prepared from the blood of 6 foreign healthy adult subjects (1 male and 5 female subjects³⁸⁾) was spiked with 25 to 400 µg/mL of sugammadex, sugammadex had no effect on the platelet aggregation induced by adenosine diphosphate (ADP), collagen, or the thrombin receptor activating peptide (TRAP) (Reference data 5.3.2.3.4).

When human plasma collected from healthy adult subjects³⁹⁾ was spiked with 50 to 500 µg/mL of sugammadex or Related Substance Org48302, the APTT and PT were increased dose-dependently and the effects of Related Substance Org48302 (APTT, increases of 0%-16.7%; PT, increases of 0%-15.0%) were smaller than those of sugammadex (APTT, increases of 9.8%-43.4%; PT, increases of 8.0%-32.6%). While sugammadex (50-200 µg/mL) had no effect on factor Xa generation in the extrinsic pathway (factor Xa generation assay using PT reagent), sugammadex (50-400 µg/mL) dose-dependently inhibited factor Xa generation (factor Xa generation assay using APTT reagent), one-step human PiCT (Prothorombinase induced Clotting Time) using the purified human factor Xa, and thrombin generation in the intrinsic pathway.⁴⁰⁾ The effects of 200 and 400 µg/mL sugammadex on the APTT and PT were reduced in the presence of rocuronium (0-377.6 µM) or vecuronium (0-71.7 µM) and disappeared at an equimolar ratio of sugammadex to rocuronium or vecuronium. When human plasma collected from perioperative patients³⁹⁾ was spiked with 400 µg/mL sugammadex, the APTT and PT were prolonged by 26.6% to 78.6% and 23.7% to 39.5%, respectively, which were not substantially different from the results with plasma collected from foreign healthy adult subjects (increases of 39.6% and 33.3%, respectively), though the data variability was high (Reference data 5.3.2.3.5).

4.(i).A.(1).5) Pharmacodynamic interactions with anticoagulants and antithrombotics

When human plasma collected from patients receiving a vitamin K antagonist (acenocoumarol

³⁸⁾ One female subject had missing data for the thrombin receptor activating peptide (TRAP).

³⁹⁾ Pooled plasma collected in the Netherlands was used and the demographics (race, etc.) of donors are unknown.

⁴⁰⁾ In human plasma, the ecarin clotting time or thrombin generation was not affected by sugammadex (100-500 or 200-600 µg/mL, respectively). There was no trend for a difference in the effect of 50 to 500 µg/mL of sugammadex on the APTT between antithrombin- and heparin cofactor II-deficient human plasma and non-deficient human plasma and the effects of 100 µg/mL sugammadex on the PT-INR did not show an anti-phospholipid profile as observed in lupus anticoagulant-positive human plasma. The effects of 200 µg/mL sugammadex on the APTT were similar either in the presence or absence of calcium (25 or 50 mM) or calcium/magnesium (25 mM each) and between factor V-deficient human plasma and non-deficient human plasma and the effects on the PT-INR were independent of activated factor VII concentration. The effects of 400 µg/mL sugammadex on the PT-INR were similar between factor IX-deficient human plasma and non-deficient human plasma. Based on these results, the applicant discussed that increases in the APTT and PT-INR in samples spiked with sugammadex are not associated with its effects on phospholipids, calcium or magnesium concentration, or coagulation inhibitors (antithrombin, heparin cofactor II), but due to decreased generation and activity of factor Xa.

or phenprocoumon, both unapproved in Japan)³⁹⁾ was spiked with 50 and 200 µg/mL of sugammadex, the APTT and PT were prolonged additively. In human plasma with a PT-INR of 4.37, sugammadex (200 µg/mL) prolonged the APTT and PT by 50% and 22%, respectively (20.0 and 37.5 seconds, respectively). When human plasma collected from foreign healthy adult subjects was spiked with sugammadex (50-400 µg/mL) and an irreversible factor Xa inhibitor, unfractionated heparin (0.15 and 0.30 U/mL), enoxaparin (5 and 10 µg/mL), or fondaparinux (0.3 and 0.6 µg/mL), the APTT was prolonged additively. Likewise, sugammadex and a reversible factor Xa inhibitor, rivaroxaban (100 and 200 ng/mL, unapproved in Japan) or a reversible thrombin inhibitor, dabigatran (106 and 212 ng/mL, unapproved in Japan) prolonged the APTT synergistically (by up to 79.5%) (Reference data 5.3.2.3.5).

4.(i).A.(2) Pharmacokinetic investigation in healthy adult volunteers

4.(i).A.(2).1 Single intravenous dose trial in Japanese and Caucasian subjects

Following single intravenous doses of 1.0, 8.0, and 16.0 mg/kg of sugammadex in Japanese and Caucasian healthy adult subjects (14 subjects each [7 male and 7 female subjects]), the pharmacokinetic parameters of unchanged sugammadex in plasma were as shown in the following table. No ethnic differences were observed. In the Japanese subjects, the AUC_{0-∞} increased dose-dependently and the t_{1/2β} and CL were almost constant, regardless of dose (5.3.3.3.1, Trial 19.4.102).

Table. Pharmacokinetic parameters of unchanged sugammadex in plasma following single intravenous doses of sugammadex in Japanese and Caucasian subjects (5.3.3.3.1, Trial 19.4.102)

Pharmacokinetic parameter		Japanese subjects (n = 14)			Caucasian subjects (n = 14)		
		1 mg/kg	8 mg/kg	16 mg/kg	1 mg/kg	8 mg/kg	16 mg/kg
AUC _{0-∞} (µg·min/mL)	Geometric mean	561	4604	9670	530	4828	10 185
	CV (%)	14.2	10.0	13.5	17.2	12.6	14.0
CL (mL/min)	Geometric mean	106	103	98.4	125	109	104
	CV (%)	16.7	9.02	15.5	17.7	13.5	10.9
t _{1/2β} (min)	Geometric mean	107	132	143	101	161	181
	CV (%)	13.9	17.5	22.5	16.7	39.9	30.5
V _{ss} (mL)	Geometric mean	12 071	11 799	11 370	14 053	13 246	12 617
	CV (%)	13.5	15.5	15.0	19.1	21.0	11.2
Urinary excretion up to 24 hours (% of dose)	Geometric mean	59.1	71.3	77.0 ^{a)}	67.6	72.1	74.2
	CV (%)	40.1	21.4	12.4	17.1	15.5	10.7

CV: Geometric coefficient of variation, a) n = 13

4.(i).A.(2).2 Single intravenous dose trials in foreign subjects

Following single intravenous doses of 0.1 to 8.0 mg/kg of sugammadex in 17 foreign healthy adult male non-anesthetized subjects, the t_{1/2β} (geometric mean) of unchanged sugammadex in plasma was 94.5 to 128 minutes (65.8 minutes following 0.1 mg/kg of sugammadex), the CL (geometric mean) was 99.2 to 138 mL/min, and the urinary excretion up to 24 hours post-dose (geometric mean) was 58.8% to 80.4% (the urinary excretion following 0.1-0.5 mg/kg of sugammadex could not be calculated), which were almost constant, regardless of dose. Following single intravenous doses of 0.1 to 8.0 mg/kg of sugammadex at 3 minutes after 0.6

mg/kg of rocuronium in 10 foreign healthy adult male subjects under balanced anesthesia, the $t_{1/2\beta}$ (geometric mean) of unchanged sugammadex in plasma was 85.1 to 119 minutes and the CL (geometric mean) was 74.7 to 118 mL/min, which were almost comparable to those in conscious (non-anesthetized) subjects. On the other hand, with increasing dose of sugammadex, the plasma CL of rocuronium decreased and the urinary excretion of rocuronium tended to increase (5.3.3.1.2, Trial 19.4.101).

Following single intravenous doses of 32.0, 64.0, and 96.0 mg/kg of sugammadex (Batch AE containing █% of Org48302) in 12 foreign healthy adult subjects (6 male and 6 female subjects), the $AUC_{0-\infty}$ values of unchanged sugammadex and Org48302 in plasma increased almost dose-dependently and the CL values of unchanged sugammadex and Org48302 were 104 to 111 and 133 to 135 mL/min, respectively, the $t_{1/2\beta}$ values were 187 to 260 and 109 to 123 minutes, respectively, and the urinary excretions up to 48 hours post-dose (% of the dose) were 90% to 93% and 80% to 87%, respectively (5.3.3.1.4, Trial 19.4.106).

Following a single intravenous dose of 4.0 mg/kg of ^{14}C -sugammadex in 6 foreign healthy adult male subjects, 96.1% of the administered radioactivity was excreted in urine up to 144 hours post-dose and excretion via feces or expired air was $\leq 0.02\%$ of the administered radioactivity. Most of the radioactivity in urine or plasma (about 95% in urine, about 100% in plasma) was attributed to unchanged sugammadex and 2 different █ related substances (Related Substance E and Related Substance I) were detected (5.3.3.1.5 and 5.3.3.1.6, Trial 19.4.107).

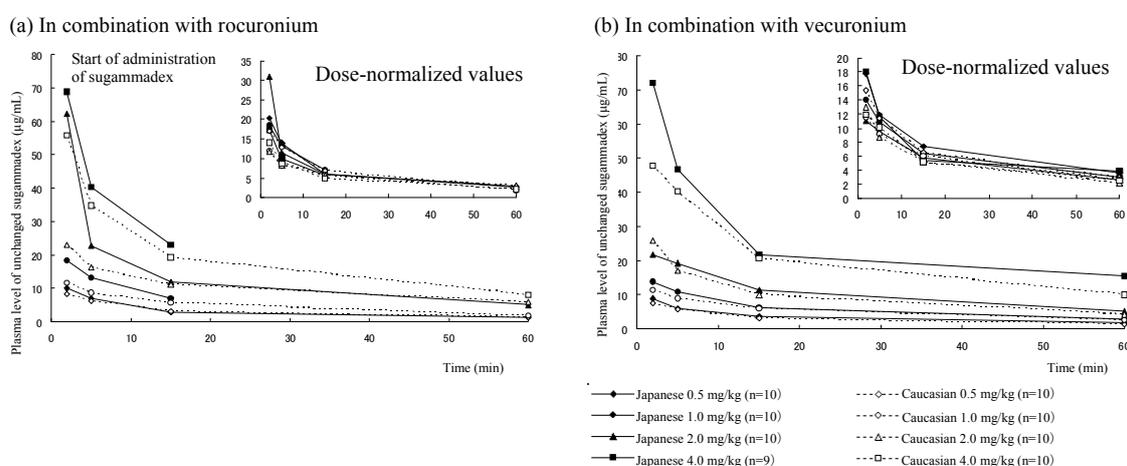
A single intravenous dose of 16.0, 20.0, or 32.0 mg/kg of sugammadex was administered at the same time as rocuronium 1.2 mg/kg or vecuronium 0.1 mg/kg in 16 foreign healthy adult subjects (10 male and 6 female subjects) under balanced anesthesia or unanesthetized conditions. The plasma molar concentration ratio of unchanged sugammadex to rocuronium or vecuronium increased over time, indicating that rocuronium and vecuronium plasma concentration decreased faster than that of unchanged sugammadex (5.3.3.1.7, Trial 19.4.108).

4.(i).A.(3) Pharmacokinetic investigation in surgical patients

4.(i).A.(3).1 Phase II trial in Japanese and Caucasian subjects (5.3.5.1.8, Trial 19.4.208)

Japanese and Caucasian patients with ASA Class 1-3 scheduled for surgical procedures in the supine position under sevoflurane anesthesia with an anticipated duration of about 1.5 to 3 hours (98 Japanese subjects and 98 Caucasian subjects included in pharmacokinetic assessment) intravenously received 0.9 mg/kg rocuronium or 0.1 mg/kg vecuronium for intubation with

maintenance doses of 0.1 to 0.2 mg/kg rocuronium or 0.02 to 0.04 mg/kg vecuronium as required (the maintenance doses of vecuronium were 0.02-0.03 mg/kg⁴¹⁾ for Caucasian patients). Then, single intravenous doses of 0.5, 1.0, 2.0, and 4.0 mg/kg of sugammadex were administered at the reappearance of T₂.⁴²⁾ Plasma levels of unchanged sugammadex increased dose-dependently and Japanese subjects had a 23% higher mean plasma level than in Caucasian subjects, but the time courses of plasma levels of unchanged sugammadex were as shown in the following figures, showing no major differences between Japanese and Caucasian subjects. Plasma rocuronium and vecuronium levels increased immediately after administration of sugammadex, but no major changes were observed in the subsequent time courses.



Figures. Time course of plasma levels of unchanged sugammadex following single intravenous doses of sugammadex at the reappearance of T₂ after administration of rocuronium (a) or vecuronium (b) in Japanese and Caucasian patients under balanced anesthesia (Median) (5.3.5.1.8, Trial 19.4.208)

4.(i).A.(4) Intrinsic factor pharmacokinetic trials

4.(i).A.(4).1 Trial in patients with impaired renal function (5.3.5.1.17, Trial 19.4.304)

Foreign subjects with impaired renal function (ASA Class 1-3, creatinine clearance [CL_{Cr}] <30 mL/min, 13 subjects included in pharmacokinetic assessment) and foreign subjects with normal renal function (ASA Class 1-2, CL_{Cr} ≥80 mL/min, 13 subjects included in pharmacokinetic assessment) received a single intravenous dose of 2.0 mg/kg of sugammadex at the reappearance of T₂ following a single intravenous dose of 0.6 mg/kg of rocuronium for intubation under balanced anesthesia. In subjects with impaired renal function relative to subjects with normal renal function, the AUC values (geometric mean) of unchanged sugammadex and rocuronium in plasma were about 17-fold and about 4-fold higher, respectively, the CL values (geometric mean) were reduced about 16-fold and about 4-fold,

⁴¹⁾ As the approved maintenance doses of vecuronium are different between Japan and overseas, maintenance doses were chosen according to the approved doses in each country.

⁴²⁾ T₂ (second twitch): amplitude of the second response to TOF stimulation (train-of-four: four consecutive square wave supra-maximal stimuli of 0.2 msec. duration delivered at a frequency of 2 Hz) using a neuromuscular monitor, expressed as percentage of control T₁ (first twitch: amplitude of the first response to TOF stimulation) (%). The reappearance of T₂ was defined as the first time point, from a sequence of three time points, that the T₂ response is recorded.

respectively, and the $t_{1/2\beta}$ values (geometric mean) were increased about 15-fold and about 3-fold, respectively. In 9 subjects with impaired renal function who underwent hemodialysis within 72 hours postoperatively (high flux membrane, 2 subjects; low flux membrane, 7 subjects), the ratio of plasma concentration of unchanged sugammadex after hemodialysis to that before hemodialysis was 0.57 to 0.60 for a high flux membrane and 0.87 to 1.20 for a low flux membrane.

4.(i).A.(4).2 Trial in geriatric patients (5.3.5.1.18, Trial 19.4.305)

Geriatric and adult foreign subjects with ASA Class 1-3 (75 subjects included in pharmacokinetic assessment: 24 subjects at 18-64 years of age, 32 subjects at 65-74 years of age, 19 subjects at ≥ 75 years of age) received a single intravenous dose of 2.0 mg/kg of sugammadex at the reappearance of T₂ after an intravenous dose of 0.6 mg/kg rocuronium for intubation with maintenance doses of 0.15 mg/kg rocuronium as required, under balanced anesthesia. The $t_{1/2}$ values (median) of unchanged sugammadex in plasma, calculated from the population pharmacokinetic analysis assuming a 3-compartment model using the median age, body weight, and CL_{cr} of each age group (18-64 years of age, 65-74 years of age, ≥ 75 years of age) (the CL_{cr} was 104, 84.8, and 58.6 mL/min, respectively), were 141, 192, and 273 minutes, respectively.

4.(i).A.(5) Other clinical pharmacology trials

4.(i).A.(5).1 Effects on QT/QTc interval

When foreign healthy adult male and female subjects (61 subjects included in pharmacokinetic assessment) received single intravenous doses of 4.0 and 32.0 mg/kg of sugammadex, 400 mg of moxifloxacin, and saline in a crossover trial, 4.0 and 32.0 mg/kg of sugammadex did not lead to QT/QTc interval prolongation (5.3.3.1.3, Trial 19.4.105).

When foreign healthy adult male and female subjects (83 subjects included in pharmacokinetic assessment) received single intravenous doses of 4.0 and 32.0 mg/kg of sugammadex alone, 32.0 mg/kg of sugammadex in combination with 1.2 mg/kg of rocuronium or 0.1 mg/kg of vecuronium, 400 mg of moxifloxacin, and saline in a crossover trial, 4 and 32 mg/kg of sugammadex alone and 32 mg/kg of sugammadex in combination with rocuronium or vecuronium had no QT/QTc interval prolongation effects (5.3.3.1.8, Trial 19.4.109).

4.(i).A.(5).2 Effects on blood coagulation system

Following single intravenous doses of 4.0 and 16 mg/kg of sugammadex in 7 foreign healthy adult subjects, 4.0 mg/kg of sugammadex prolonged the APTT and PT by up to 17% and 11%, respectively, and 16 mg/kg of sugammadex prolonged both the APTT and PT by up to 22%, compared with saline. In all cases, this prolongation was observed within 30 minutes after

sugammadex administration and was not noted at 60 minutes post-dose (5.3.3.1.11, Trial 19.4.115).

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Re-administration of neuromuscular blocking agents after sugammadex administration

The proposed package insert includes a precaution regarding waiting times for re-administration of neuromuscular blocking agents (rocuronium or vecuronium) after sugammadex administration. PMDA asked the applicant to explain its necessity and rationale.

The applicant explained as follows:

It has been reported that endotracheal reintubation was performed postoperatively in 2% to 19% of inpatients managed in the intensive care unit (ICU) (Glanemann M et al. *J ClinAnesth.* 2001;13: 377-382.). The applicant considered that re-administration of a neuromuscular blocking agent (endotracheal reintubation) will be required in the cases where pulmonary complications or post-operative bleeding complications occur immediately after the operation. Using the half-life of unchanged sugammadex in plasma following sugammadex administration, times required for a sufficiently large molar excess (≥ 8 -fold) of a steroidal neuromuscular blocking agent (rocuronium or vecuronium) relative to sugammadex in plasma, were predicted. As a result, waiting times of 2 to 16 hours were recommended for patients with normal renal function, depending on the doses of sugammadex and a neuromuscular blocking agent, and predicted times would be doubled in patients with mild renal impairment and tripled in patients with moderate renal impairment. However, since the EU regulatory agency instructed the sponsor to recommend a single waiting time, regardless of the dose of sugammadex or a neuromuscular blocking agent or renal function, a waiting time of 24 hours was recommended in the EU. In Japan, taking account of the results of a study to assess the re-use of a neuromuscular blocking agent after sugammadex administration conducted after the EU approval (Reference data 5.3.3.1.10, Trial 19.4.113) and moreover, based on predictions from simulation with the PK/PD model,⁴³⁾ the recommended waiting time for re-administration of neuromuscular blocking agents after sugammadex administration has been changed. The recommended waiting time has been determined so that re-administration of a neuromuscular blocking agent after sugammadex administration would be as efficacious as when the neuromuscular blocking agent is used alone (as measured by the time to onset of action, i.e. the time to a T_4/T_1 ratio of 0.1). Namely, the recommended waiting times following up to 4 mg/kg

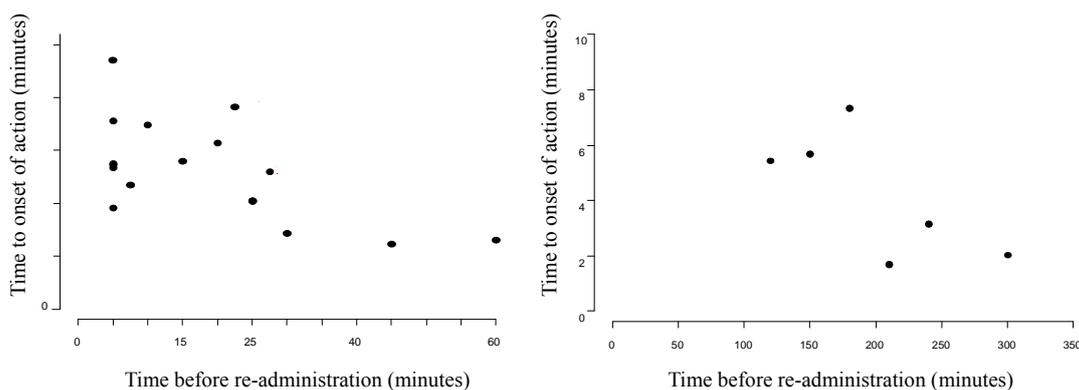
⁴³⁾ After the EU approval, the PK/PD model was revised to evaluate the efficacy of re-administration of rocuronium after sugammadex administration.

of sugammadex are 15 minutes for re-administration of 0.9 mg/kg rocuronium and 4 hours for re-administration of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium. The recommended waiting time following 16 mg/kg of sugammadex (immediate reversal) is 24 hours. If neuromuscular blockade is required before the recommended waiting time has passed, a nonsteroidal neuromuscular blocking agent (suxamethonium) should be used.

PMDA asked the applicant to explain the details of the results from Foreign Trial 19.4.113 (Reference data 5.3.3.1.10).

The applicant explained as follows:

In Foreign Trial 19.4.113 (Reference data 5.3.3.1.10), 22 foreign healthy adult subjects received 4.0 mg/kg sugammadex at 1-2 PTCs⁴⁴⁾ after administration of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium, and then, 1.2 mg/kg rocuronium or 0.1 mg/kg vecuronium at 5 to 60 minutes or 2 to 5 hours, respectively, after sugammadex administration. As a result, the times to the onset of neuromuscular blockade (the times to a T_4/T_1 ratio of 0.1 after re-administration of a neuromuscular blocking agent) were as shown in the following figures. The time to onset of action after re-administration of 1.2 mg/kg rocuronium or 0.1 mg/kg vecuronium was 1.23 to 4.72 or 1.68 to 7.35 minutes, respectively, and the duration of action (the time to recovery of T_1 to 25%) was 17.7 to 46.0 or 24.2 to 31.4 minutes, respectively (excluding 2 subjects with incomplete neuromuscular blockade from 6 subjects treated with vecuronium). There were no events of safety concern in these subjects.



Figures. Observed times to onset of neuromuscular blockade (time to a T_4/T_1 ratio of 0.1 after re-administration of a neuromuscular blocking agent) in individual foreign healthy adult subjects who received 4.0 mg/kg sugammadex at 1-2 PTCs following administration of 0.6 mg/kg rocuronium (left) or 0.1 mg/kg vecuronium (right), and then 1.2 mg/kg rocuronium or 0.1 mg/kg vecuronium at 5-60 minutes or 2-5 hours, respectively, after sugammadex administration (5.3.3.1.10, Trial 19.4.113)

⁴⁴⁾The occurrence of 1-2 PTCs (post-tetanic count) represents a situation of profound neuromuscular blockade, i.e. zero responses to TOF stimulation (T_1 - T_4 , 0%) and 1-2 responses to post-tetanic single-twitch stimulation (15 post-tetanic 1 Hz stimuli) 3 seconds after tetanic stimulation (50 Hz, 5 seconds), using a neuromuscular monitor.

PMDA asked the applicant to explain about patients who were actually re-administered a steroidal or non-steroidal neuromuscular blocking agent after sugammadex administration in clinical trials involving patients.

The applicant explained as follows:

In pooled Japanese and foreign phase II and III trials,³⁰⁾ a neuromuscular blocking agent was re-administered in 9 patients (all foreign patients) as shown in the following table, but none of the patients were re-administered rocuronium or vecuronium at the timing and doses as specified in the proposed package insert.

Table. Patients re-administered a neuromuscular blocking agent after sugammadex administration in pooled Japanese and foreign phase II and III trials (all foreign patients)

Trial Number	Patient demographics	Administered dose of sugammadex (Initially administered neuromuscular blocking agent)	Re-administration of neuromuscular blocking agent			
			Name of drug	Dose	Time before re-administration ^{a)}	Time to onset of action ^{b)}
Trial 19.4.205 (5.3.5.1.5)	40-year-old female, Body weight 91 kg	8.0 mg/kg (Rocuronium)	Rocuronium	0.2 mg/kg (20 mg) × 2	1 hour 44 minutes, 1 hour 48 minutes	Neuromuscular blockade was not produced.
Trial 19.4.207 (5.3.5.1.7)	67-year-old male, Body weight 64 kg	0.3 mg/kg (Rocuronium)	Cisatracurium	0.4 mg/kg (25 mg)	1 hour 17 minutes	5 minutes
	44-year-old male, Body weight 97 kg	8.0 mg/kg (Pancuronium)	Cisatracurium ^{d)}	61.9 µg/kg (6 mg)	1 hour 11 minutes	4.5 minutes
	70-year-old male, Body weight 90 kg	6.0 mg/kg (Pancuronium)	Cisatracurium	0.1 mg/kg (10 mg)	49 minutes	3.1 minutes
	50-year-old male, Body weight 113 kg	2.0 mg/kg (Rocuronium)	Cisatracurium	53.1 µg/kg (6 mg)	42 minutes	Complete neuromuscular blockade was not achieved (up to ^{c)} 75%)
	52-year old male, Body weight 74 kg	4.0 mg/kg (Vecuronium)	Cisatracurium	54.1 µg/kg (4 mg)	51 minutes	3.6 minutes
Trial 19.4.209 (5.3.5.1.9)	58-year-old female, Body weight 74 kg	8.0 mg/kg (Rocuronium)	Rocuronium	0.3 mg/kg (20 mg)	37 minutes	Neuromuscular blockade was not produced.
	61-year-old male, Body weight 97 kg	2.0 mg/kg (Vecuronium)	Cisatracurium ^{d)}	206.2 µg/kg (20 mg)	11 minutes	1.7 minutes
	33-year-old male, Body weight 95 kg	3.7 mg/kg (Rocuronium)	Suxamethonium	1.1 mg/kg (100 mg)	4 minutes	1.0 minute

a) Time after sugammadex administration, b) Time to T₁ of 0 after re-administration of neuromuscular blocking agent

c) 100% minus T₁ twitch height

d) Although cisatracurium was administered multiple times (2 or 5 times), the results after the first administration only are presented.

PMDA considers as follows:

The applicant's explanation that a precaution will be included, assuming a situation where re-administration of a neuromuscular blocking agent after sugammadex administration is required in routine clinical practice, is understood. Meanwhile, there has been no patient who was actually re-administered a steroidal neuromuscular blocking agent at the timing recommended by the applicant and a clinical trial to assess the re-use of rocuronium at the approved doses in Japan (0.6-0.9 mg/kg) has not been conducted. Therefore, at present, it is difficult to specify a waiting time for re-administration of a steroidal neuromuscular blocking agent, based on scientific evidence.

Taking also into account that sugammadex may also affect the time to the onset of action of a non-steroidal neuromuscular blocking agent suxamethonium [see "3.(i).A.(1).3) Action of non-steroidal neuromuscular blocking agent after reversal of rocuronium-induced neuromuscular block with sugammadex"], PMDA will finalize a specific precaution statement regarding re-administration of neuromuscular blocking agents after sugammadex administration, based on comments from the Expert Discussion.

4.(i).B.(2) Effects of sugammadex on blood coagulation system

Since sugammadex prolongs the APTT and PT, PMDA asked the applicant to explain the clinical effects of sugammadex on blood coagulation system.

The applicant explained as follows:

When human plasma samples were spiked *in vitro* with 50 and 200 µg/mL sugammadex (50 and 200 µg/mL sugammadex are the C₀ values of unchanged sugammadex in plasma at 4 and 16 mg/kg, respectively) (Reference data 5.3.2.3.5), the APTT and PT values were as shown in the following table and the effects of sugammadex were smaller compared with those of anticoagulants and antithrombotics.

Table. Effects of sugammadex spiked in various human plasma samples (obtained from foreign subjects) on APTT and PT (Reference data 5.3.2.3.5)

Sample (plasma)	Parameter	Clotting time (seconds) (Percent prolongation ^{a)} %)		
		Un-spiked	Sugammadex 50 µg/mL ^{b)}	Sugammadex 200 µg/mL ^{b)}
Healthy adults	APTT	38.1	41.9 (9.8)	49.1 (28.9)
	PT	13.2	14.3 (8.0)	15.8 (19.3)
Patients receiving vitamin K antagonists (PT-INR, 2.3-3.7)	APTT	51.6-56.7	58.4-63.8 (12.4-14.0)	71.7-75.5 (33.2-39.0)
	PT	27.0-40.7	29.3-44.6 (6.9-9.6)	34.9-50.0 (22.7-29.3)
Patients receiving vitamin K antagonists (PT-INR, 4.3)	APTT	75.2	95.2 (26.5)	112.7 (49.8)
	PT	46.8	51.8 (10.6)	57.1 (22.0)
Unfractionated heparin (0.15 U/mL)	APTT	45.6	52.0 (14.1)	57.9 (27.1)
Enoxaparin (10 µg/mL)	APTT	84.6	90.9 (7.5)	103.2 (22.1)
Fondaparinux (0.6 µg/ml)	APTT	43.7	48.8 (11.8)	52.9 (21.2)
Dabigatran ^{c)} (212 ng/ml)	APTT	62.4	68.7 (10.0)	80.6 (29.2)
Rivaroxaban ^{c)} (200 ng/ml)	APTT	56.7	65.5 (15.5)	86.2 (51.9)

Mean values of APTT (Activated partial thromboplastin time) and PT (prothrombin time)

The effects of anticoagulants and antithrombotics were investigated for APTT only and the results at the higher of the two concentrations only are listed.

a) Percent prolongation vs. un-spiked sample (%)

b) Sugammadex 50 and 200 µg/mL are the plasma concentrations of unchanged sugammadex immediately after intravenous administration of sugammadex 4 and 16 mg/kg, respectively (C₀) in Japanese and Caucasian healthy adult subjects (5.3.3.3.1, Trial 19.4.102)

c) Unapproved in Japan

Then, the applicant explained as follows:

The effects of sugammadex on the APTT and PT are reduced in the presence of rocuronium or vecuronium, and immediately after sugammadex administration (at a molar ratio of sugammadex to rocuronium or vecuronium of about 10), the change caused by sugammadex alone is predicted to decrease by about a 10% (Reference data 5.3.2.3.5). In a study to investigate the effects on hemostasis parameters in foreign healthy adult subjects (Reference data 5.3.3.1.11, Trial 19.4.115), the prolongation of the APTT and PT was observed only within 30 minutes after sugammadex administration and its effects were transient. Generally, anticoagulants and antithrombotics are used post-operatively following achievement of hemostasis. Therefore, sugammadex is unlikely to increase the risk of bleeding. However, since sugammadex at ≥ 4.0 mg/kg may worsen coagulopathies in patients on vitamin K antagonists and at a PT-INR above 3.5, patients with hereditary vitamin K dependent clotting factor deficiencies, hepatic impairment patients with coagulopathies, etc., monitoring of coagulation parameters for patients with coagulopathies will be recommended in “Important Precautions” of the package insert.

The applicant also explained about adverse events related to bleeding complications⁴⁵⁾ reported in clinical trials as follows:

⁴⁵⁾ Adverse events were identified by the MedDRA Preferred Terms (PT): postoperative bleeding, post procedural haemorrhage, incision site haemorrhage, wound haemorrhage, haemorrhage, blood urine present, haematuria, catheter site haemorrhage, , gastrointestinal haemorrhage, intra-abdominal haemorrhage, intraventricular haemorrhage, bladder tamponade, vaginal haemorrhage, haemoptysis, haematochezia, muscle haemorrhage, rectal haemorrhage, tooth socket haemorrhage, ureteric haemorrhage, urinary bladder haemorrhage, mouth haemorrhage, epistaxis, haemorrhage subcutaneous, subcutaneous haematoma, haematoma, periorbital haematoma, incision site haematoma, abdominal haematoma, petechiae, post procedural haematoma, ecchymosis, haemoglobin decreased, haematocrit decreased, red blood cell count decreased, anaemia, and haemorrhagic anaemia.

In pooled Japanese and foreign phase II and III trials,³⁰⁾ adverse events related to bleeding complications occurred in 10.2% of sugammadex-treated subjects (177 of 1738 subjects; mild, 5.3%; moderate, 3.7%; severe, 1.2%), including 17 serious cases, but all of these events resolved except for 1 case with an unknown outcome. In pooled Japanese and foreign phase II and III trials with a placebo group,³¹⁾ adverse events related to bleeding complications occurred in 7.6% (48 of 630 subjects) of the sugammadex group and 6.2% (8 of 130 subjects; mild, 2.3%; moderate, 2.3%, severe, 1.5%) of the placebo group. In foreign phase III trials with a neostigmine group (5.3.5.1.13, Trial 19.4.301; 5.3.5.1.15, Trial 19.4.302), adverse events related to bleeding complications occurred in 6.7% (12 of 179 subjects) of the sugammadex group and 7.8% (13 of 167 subjects; mild, 6.0%, moderate, 1.2%; severe, 0.6%) of the neostigmine group. No major differences in the incidence were noted between the sugammadex group and the placebo or neostigmine group and there was no dose-dependent increase in the incidence. In bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209), adverse events related to bleeding complications occurred in 24.9% of the sugammadex group (44 of 177 subjects; mild, 22.0%; moderate, 2.8%) and 10.0% of the placebo group (2 of 20 subjects; mild, 10.0%) in Japanese subjects and 7.8% of the sugammadex group (14 of 179 subjects; mild, 3.4%; moderate, 3.4%; severe, 1.1%) and 0% of the placebo group (0 of 20 subjects) in Caucasian subjects, showing a trend towards a higher incidence with both sugammadex and placebo in Japanese subjects compared to Caucasian subjects. However, in Japanese subjects, no severe events were reported and a causal relationship to the drug was denied for all of 5 moderate events (epistaxis [2 subjects], haemorrhage subcutaneous [1 subject], post procedural haemorrhage [1 subject], anaemia [1 subject]) and the outcome was reported as resolved or improved except for 2 cases (haemorrhage subcutaneous [1 subject], anaemia [1 subject]). Therefore, bleeding complications associated with sugammadex are unlikely to become a clinically relevant problem.

PMDA asked the applicant to explain the occurrence of bleeding complications in patients with coagulopathies.

The applicant explained as follows:

In pooled Japanese and foreign phase II and III trials,³⁰⁾ 3 of 6 patients with a history of coagulopathies⁴⁶⁾ experienced adverse events related to bleeding complications (anaemia, anaemia postoperative, and haematuria, one case each), but none of these events were severe. A causal relationship was denied and all events resolved or improved without treatment.

⁴⁶⁾ Patients with a history of coagulopathies were identified using the MedDRA High Level Group Term (HLGT): “coagulopathies and bleeding diatheses (excl thrombocytopenic)” or High Level Terms (HLT): “coagulation disorders congenital” and “coagulation and bleeding analyses.”

PMDA considers as follows:

Since the *in vitro* effects of sugammadex on coagulation variables were smaller compared to those of anticoagulants and antithrombotics and its effects were transient, at present, the risk of bleeding associated with sugammadex is unlikely to cause a clinically relevant problem, but caution is needed when sugammadex is used in patients with coagulopathies. The risk of bleeding associated with sugammadex needs to be investigated after the market launch.

4.(i).B.(3) Effects of pharmacokinetics in special populations on efficacy and safety

PMDA asked the applicant to explain the effects of the pharmacokinetics of sugammadex in patients with impaired renal or hepatic function on its efficacy and safety.

The applicant explained as follows:

Foreign subjects with severe renal impairment (CL_{cr} <30 mL/min) or normal renal function (CL_{cr} ≥80 mL/min) received 2.0 mg/kg of sugammadex at the reappearance of T₂ following a neuromuscular blockade induced by an intubating dose of 0.6 mg/kg of rocuronium under balanced anesthesia (5.3.5.1.17, Foreign Trial 19.4.304). As a result, in subjects with severe renal impairment relative to subjects with normal renal function, the CL of unchanged sugammadex (geometric mean) was reduced about 16-fold and the AUC (geometric mean) was about 17-fold higher while there were no major differences in the plasma concentrations of unchanged sugammadex up to 1 hour after sugammadex administration. The time from start of administration of sugammadex to recovery of the T₄/T₁ ratio⁴⁷⁾ to 0.9 (mean ± SD) was 2 minutes 00 second ± 43 seconds in subjects with severe renal impairment (n = 15), which was almost comparable to 1 minute 39 seconds ± 38 seconds in subjects with normal renal function (n = 14). The incidence of adverse events was 53.3% (8 of 15 subjects) in subjects with severe renal impairment and 80.0% (12 of 15 subjects) in subjects with normal renal function and there were no safety problems in subjects with severe renal impairment.

Although the pharmacokinetics, efficacy, and safety of sugammadex in patients with impaired hepatic function have not been investigated, there were no particular safety problems in 15 subjects judged to have serious hepatic impairment⁴⁷⁾ in Japanese and foreign phase II and III trials. In 3 trials where 2.0 mg/kg of sugammadex was to be administered at the reappearance of T₂ following 0.6 mg/kg of rocuronium (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.18, Trial 19.4.305; 5.3.5.1.14, Trial 19.4.310), the geometric mean time from start of administration of

⁴⁷⁾ Among 77 subjects identified by the Standardized MedDRA Query (SMQ) “Hepatic disorders,” 15 subjects with baseline clinical chemistry values (bilirubin, ALT (GPT), AST (GOT), or γ-GPT) outside the safe range were identified. Six of the 15 subjects had received the recommended clinical dose of sugammadex, of whom 5 subjects excluding 1 subject with concurrent renal impairment were analyzed.

sugammadex to recovery of the T_4/T_1 ratio¹⁴⁾ to 0.9 (Min.-Max.) in 5 subjects judged to have serious hepatic impairment⁴⁷⁾ was 2 minutes: 24 seconds (1 minute: 06 seconds - 5 minutes: 06 seconds), which was not much different from 2 minutes: 00 second (42 seconds - 12 minutes: 00 second) in other subjects.

Furthermore, excretion of sugammadex may be delayed depending on CL_{cr} in geriatric patients. When foreign geriatric and adult subjects (48 subjects at <65 years of age, 62 subjects at 65-74 years of age, 40 subjects at ≥75 years of age) received 2.0 mg/kg of sugammadex at the reappearance of T₂ following an intubating dose of 0.6 mg/kg of rocuronium with maintenance doses of 0.15 mg/kg as required under general anesthesia (5.3.5.1.18, Trial 14.9.305), the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio¹⁴⁾ to 0.9 (including imputed data,⁴⁸⁾ mean ± SD) was 2 minutes 36 seconds ± 1 minute 37 seconds in subjects at <65 years of age, 2 minutes 44 seconds ± 1 minute 18 seconds in subjects at 65-74 years of age, and 3 minutes 48 seconds ± 2 minutes 01 second in subjects at ≥75 years of age, showing a trend towards slightly slower recovery in geriatric subjects, but there were no safety problems.

Based on the above, the applicant considered as follows:

No sugammadex dose adjustment is required in renally- or hepatically-impaired patients or geriatric patients. However, especially for patients with severe renal impairment, although it has been indicated that sugammadex may be efficiently removed via hemodialysis using a high flux membrane [see “4.(i).A.(1).2) *In vitro* study on the dialysability of sugammadex and 4.(i).A.(4).1) Trial in patients with impaired renal function”], as effective dialysis has not consistently been demonstrated, sugammadex should be administered with care after carefully determining the need for sugammadex.

PMDA considers as follows:

It is necessary to carefully determine the need for sugammadex in patients with renal or hepatic impairment and geriatric patients and at present, there will be no clinically relevant problem if careful administration is advised in these patients. The safety of sugammadex in these patients should continue to be investigated after the market launch.

⁴⁸⁾ In phase III trials, two analyses were performed: one in which missing data were imputed and the other in which only observed data were used. The results of analysis using the imputed data only are presented in this report. Missing data were imputed, using the 95th percentile (P95) and the 5th percentile (P5) of the differences between the available times to recovery of the T_4/T_1 ratio to 0.9 and the available times to recovery of the T_4/T_1 ratio to 0.8 (or 0.7), as follows:

- When the time to recovery of the T_4/T_1 ratio to 0.8 was available, the time to recovery of the T_4/T_1 ratio to 0.8 plus P95 or P5 was imputed in the sugammadex or neostigmine group, respectively.
- When the time to recovery of the T_4/T_1 ratio to 0.7 was available, the time to recovery of the T_4/T_1 ratio to 0.7 plus P95 or P5 was imputed in the sugammadex or neostigmine group, respectively.
- When neither the time to recovery of the T_4/T_1 ratio to 0.8 nor the time to recovery of the T_4/T_1 ratio to 0.7 was available, P95 or P5 of the available times to recovery of the T_4/T_1 ratio to 0.9 was imputed in the sugammadex or neostigmine group, respectively.

4.(ii) Summary of clinical efficacy and safety

4.(ii).A Summary of the submitted data

This application is based on the bridging concept. Two phase II dose-finding trials of sugammadex administered at the reappearance of T₂ (shallow blockade) and at 1-2 PTCs (profound blockade) in Japanese and Caucasian patients (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) were positioned as bridging studies and the results from these trials were compared between Japanese and Caucasian subjects, which demonstrated the similarity of dose responses. Thus, it has been concluded that foreign clinical data can be extrapolated to Japan. In addition to the above-mentioned trials, 8 phase II trials in foreign patients (5.3.5.1.1, Trial 19.4.201; 5.3.5.1.2, Trial 19.4.202; 5.3.5.1.3, Trial 19.4.203; 5.3.5.1.4, Trial 19.4.204; 5.3.5.1.5, Trial 19.4.205; 5.3.5.1.6, Trial 19.4.206; 5.3.5.1.7, Trial 19.4.207; 5.3.5.1.10, Trial 19.4.210) and 11 phase III trials in foreign subjects (5.3.5.1.11, Trial 19.4.312; 5.3.5.1.12, Trial 19.4.306; 5.3.5.1.13, Trial 19.4.301; 5.3.5.1.14, Trial 19.4.310; 5.3.5.1.15, Trial 19.4.302; 5.3.5.1.16, Trial 19.4.303; 5.3.5.1.17, Trial 19.4.304; 5.3.5.1.18, Trial 19.4.305; 5.3.5.1.19, Trial 19.4.308; 5.3.5.1.20, Trial 19.4.309; 5.3.5.2.1, Trial 19.4.311) were submitted as the efficacy and safety evaluation data in the clinical data package. As the safety evaluation data, a phase I trial in Japanese and Caucasian healthy adult subjects (5.3.3.3.1, Trial 19.4.102) and 6 phase I trials in foreign healthy adult subjects (5.3.3.1.2, Trial 19.4.101; 5.3.3.1.3, Trial 19.4.105; 5.3.3.1.4, Trial 19.4.106; 5.3.3.1.5, Trial 19.4.107; 5.3.3.1.7, Trial 19.4.108; 5.3.3.1.8, Trial 19.4.109) were submitted.

Treatment groups are expressed as “neuromuscular blocking agent-the dose of sugammadex” or “neuromuscular blocking agent-reversal agent.” With respect to adverse events, no specific mention is made of a treatment group with zero events and “adverse events for which a causal relationship to study drug could not be denied” are defined as those events classified by the investigator as “definitely related,” “probably related,” or “possibly related” on the causality scale (definitely related, probably related, possibly related, remotely related, unrelated).

4.(ii).A.(1) Phase I trials

4.(ii).A.(1).1) Phase I trial in Japanese and Caucasian healthy adult subjects (5.3.3.3.1, Trial 19.4.102 [■ 20■ to ■ 20■])

A placebo-controlled, randomized, parallel-group, double-blind comparative trial was conducted to assess the safety and pharmacokinetics of sugammadex in Japanese and Caucasian healthy adult subjects (Target sample size of 28, 14 Japanese subjects and 14 Caucasian subjects) [for pharmacokinetics, see “4.(i) Summary of human pharmacokinetic and pharmacodynamic trials”].

Single intravenous doses of 1.0, 8.0, and 16.0 mg/kg of sugammadex and placebo were to be administered. Each subject was to receive the three doses of sugammadex in ascending order separated by 1 week with interspersed placebo.

All of the 28 treated subjects were included in safety analyses.

Adverse events (including laboratory test abnormalities) occurred in 50.0% of Japanese subjects (7 of 14 subjects) and 50.0% of Caucasian subjects (7 of 14 subjects) with 1.0 mg/kg sugammadex, 57.1% of Japanese subjects (8 of 14 subjects) and 14.3% of Caucasian subjects (2 of 14 subjects) with 8.0 mg/kg sugammadex, 28.6% of Japanese subjects (4 of 14 subjects) and 21.4% of Caucasian subjects (3 of 14 subjects) with 16.0 mg/kg sugammadex, and 50.0% of Japanese subjects (7 of 14 subjects) and 14.3% of Caucasian subjects (2 of 14 subjects) with placebo, but there were no deaths or other serious adverse events.

Adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied occurred in 28.6% of Japanese subjects (4 of 14 subjects) and 28.6% of Caucasian subjects (4 of 14 subjects) with 1.0 mg/kg sugammadex, 21.4% of Japanese subjects (3 of 14 subjects) and 7.1% of Caucasian subjects (1 of 14 subjects) with 8.0 mg/kg sugammadex, 14.3% of Japanese subjects (2 of 14 subjects) and 14.3% of Caucasian subjects (2 of 14 subjects) with 16.0 mg/kg sugammadex, and 14.3% of Japanese subjects (2 of 14 subjects) and 7.1% of Caucasian subjects (1 of 14 subjects) with placebo. The main events were nausea (2 Japanese subjects and 2 Caucasian subjects at a dose of 1.0 mg/kg; 1 Japanese subject and 1 Caucasian subject at a dose of 8.0 mg/kg; 2 Japanese subjects at a dose of 16.0 mg/kg), abdominal pain NOS (2 Japanese subjects at a dose of 1.0 mg/kg; 3 Japanese subjects at a dose of 8.0 mg/kg; 1 Japanese subject on placebo), diarrhoea NOS (1 Japanese subject at a dose of 1.0 mg/kg; 2 Japanese subjects at a dose of 8.0 mg/kg), and dysgeusia (2 Caucasian subjects at a dose of 16.0 mg/kg).

There were no clinically relevant changes in vital signs (blood pressure and pulse rate), ECGs, or clinical laboratory tests.

Based on the above, the applicant explained that the tolerability of sugammadex at doses up to 16.0 mg/kg was confirmed and there were no major differences in safety between Japanese and Caucasian subjects.

4.(ii).A.(1).2) High-dose safety trial in foreign healthy adult subjects (5.3.3.1.4, Trial 19.4.106 [■ 20■ to ■ 20■])

A placebo-controlled, randomized, parallel-group, double-blind, comparative trial was conducted to assess the safety and pharmacokinetics of high doses of sugammadex in foreign healthy adult subjects (Target sample size of 12⁴⁹⁾) [for pharmacokinetics, see “4.(i) Summary of human pharmacokinetic and pharmacodynamic trials”].

Single intravenous doses of 32, 64, and 96 mg/kg of sugammadex and placebo were to be administered. Each subject was to receive the three doses of sugammadex in ascending order separated by 1 week with interspersed placebo.

All of the 13 treated subjects were included in safety analyses.

Adverse events (including laboratory test abnormalities) occurred in 38.5% (5 of 13 subjects) with 32 mg/kg sugammadex, 41.7% (5 of 12 subjects) with 64 mg/kg sugammadex, 75.0% (9 of 12 subjects) with 96 mg/kg sugammadex, and 25.0% (3 of 12 subjects) with placebo, but there were no deaths or other serious adverse events. One subject was discontinued due to adverse events (the subject was scheduled to receive 32 mg/kg sugammadex over 5 minutes, but infusion was stopped after 8.4 mg/kg sugammadex due to paraesthesia and visual disturbance). Since this subject experienced flushing and rash erythematous and had a positive intradermal test, the subject was considered to have an allergic reaction to sugammadex.

Adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied occurred in 30.8% (4 of 13 subjects) with 32 mg/kg sugammadex, 33.3% (4 of 12 subjects) with 64 mg/kg sugammadex, 75.0% (9 of 12 subjects) with 96 mg/kg sugammadex, and 8.3% (1 of 12 subjects) with placebo and the main events were dysgeusia (2 subjects at a dose of 32 mg/kg; 1 subject at a dose of 64 mg/kg; 8 subjects at a dose of 96 mg/kg), nausea (1 subject at a dose of 32 mg/kg; 2 subjects at a dose of 96 mg/kg), etc.

There were no clinically relevant changes in vital signs (blood pressure and pulse rate), ECGs, or clinical laboratory tests.

Based on the above, the applicant explained that the tolerability of sugammadex at doses up to 96 mg/kg was confirmed.

⁴⁹⁾ Due to changes to the protocol, this number was later increased by another six.

4.(ii).A.(2) Phase II bridging studies

4.(ii).A.(2).1) Bridging study for reversal of shallow neuromuscular blockade (at the reappearance of T₂) (5.3.5.1.8, Trial 19.4.208 [September 2005 to October 2006])

A placebo-controlled, randomized, parallel-group, open-label comparative trial was conducted to assess the efficacy, safety, and pharmacokinetics of sugammadex in the reversal of shallow rocuronium- or vecuronium-induced neuromuscular blockade (at the reappearance of T₂) in Japanese and Caucasian patients with ASA Class 1-3 scheduled for surgical procedures in the supine position under sevoflurane anesthesia with an anticipated duration of about 1.5 to 3 hours (Target sample size of 200, 100 Japanese subjects and 100 Caucasian subjects, 10 subjects per group)⁵⁰⁾ [for pharmacokinetics, see “4.(i) Summary of human pharmacokinetic and pharmacodynamic trials”].

Sugammadex (0.5, 1.0, 2.0, 4.0 mg/kg) or placebo was to be intravenously administered as a single bolus dose at the reappearance of T₂.⁴²⁾ For neuromuscular blockade, an intubating dose of 0.9 mg/kg rocuronium or 0.1 mg/kg vecuronium with maintenance doses of 0.1 to 0.2 mg/kg rocuronium or 0.02 to 0.04 mg/kg vecuronium as required (the maintenance doses of vecuronium were 0.02-0.03 mg/kg⁴¹⁾ for Caucasian subjects) was to be administered intravenously. Propofol was used for induction of anesthesia and anesthesia was maintained with sevoflurane and an opioid analgesic and nitrous oxide, if necessary.

A total of 196 subjects were treated and included in safety analyses. Of whom, 178 subjects were included in the Per Protocol Set (PPS) for efficacy analyses. Excluded were 18 subjects with serious protocol violations⁵¹⁾ (11 subjects with violations as to the dose of sugammadex, 10 subjects with violations as to the timing of sugammadex administration, some subjects had both violations). The number of subjects analyzed of each group was as shown in the following table. Of the PPS, 14 subjects with minor protocol violations (7 subjects treated with neostigmine,⁵²⁾ 8 subjects whose neuromuscular blockade was not measured appropriately by a neuromuscular monitor, 1 subject had both violations) were excluded from the analysis of the primary efficacy endpoint.

⁵⁰⁾ As Trial 19.4.208, Trial 19.4.208A in Japanese patients and Trial 19.4.208B in foreign (Caucasian) patients were conducted using the identical protocol.

⁵¹⁾ The volume of the drug solution to be administered, rounded to the first decimal place, was mistakenly indicated by the registration center, which resulted in “violations as to the dose of sugammadex” and each trial site was given the wrong definition of the reappearance of T₂, which resulted in “violations as to the timing of sugammadex administration (within 2 minutes after the reappearance of T₂).”

⁵²⁾ Since slow recovery from neuromuscular blockade in the placebo and low-dose sugammadex groups was anticipated, the protocol stated that the use of neostigmine (a prohibited concomitant medication) may be considered if a subject does not recover to a T₄/T₁ ratio of 0.9 within 90 minutes after sugammadex administration, though the subject will be handled as a protocol violation.

Table. Numbers of subjects included in safety analysis population and PPS of each group in phase II bridging study for reversal of shallow neuromuscular blockade (at the reappearance of T₂) (5.3.5.1.8, Trial 19.4.208)

Race	Neuromuscular blocking agent	Analysis population	Placebo group	Sugammadex groups				Total
				0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	4.0 mg/kg	
Japanese	Rocuronium	Safety	10	10	10	10	9	49
		PPS	10	5	10	10	9	44
	Vecuronium	Safety	10	10	10	9	10	49
		PPS	9	5	9	8	10	41
Caucasian	Rocuronium	Safety	10	10	9	10	10	49
		PPS	10	10	8	9	9	46
	Vecuronium	Safety	10	10	10	10	9	49
		PPS	9	10	10	9	9	47

The primary endpoint of the time from start of administration of sugammadex to recovery of the T₄/T₁ ratio¹⁴⁾ to 0.9 in the PPS was as shown in the following table.

Table. Time from start of administration of sugammadex to recovery of the T₄/T₁ ratio to 0.9 (min:sec) (PPS) in phase II bridging study for reversal of shallow neuromuscular blockade (at the reappearance of T₂) (5.3.5.1.8, Trial 19.4.208)

			Placebo group	Sugammadex groups				
				0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	4.0 mg/kg	
Japanese	Rocuronium	N	PPS	10	5	10	10	9
			Minor violation ^{a)}	3	0	0	2	0
			Missing data ^{b)}	1	0	0	1	0
			Evaluated	6	5	10	7	9
		Recovery time (min:sec)		82:05 ± 27:34	3:57 ± 2:30	2:29 ± 1:17	2:10 ± 1:14	1:51 ± 1:10
	Vecuronium	N	PPS	9	5	9	8	10
			Minor violation ^{a)}	1	2	1	0	0
			Missing data ^{b)}	1	1	0	2	0
			Evaluated	7	3	8	6	10
		Recovery time (min:sec)		83:12 ± 20:38	52:02 ± 64:55	10:38 ± 19:14	2:46 ± 0:50	2:05 ± 0:54
Caucasian	Rocuronium	N	PPS	10	10	8	9	9
			Minor violation ^{a)}	2	0	0	0	1
			Missing data ^{b)}	1	2	0	0	0
			Evaluated	7	8	8	9	8
		Recovery time (min:sec)		96:18 ± 33:08	16:18 ± 20:36	4:37 ± 5:58	1:26 ± 0:30	1:30 ± 0:24
	Vecuronium	N	PPS	9	10	10	9	9
			Minor violation ^{a)}	1	0	0	1	0
			Missing data ^{b)}	0	1	0	1	0
			Evaluated	8	9	10	7	9
		Recovery time (min:sec)		79:01 ± 25:58	35:30 ± 42:08	5:04 ± 2:23	3:25 ± 1:51	3:02 ± 2:11

Recovery time: Time from start of administration of sugammadex to recovery of the T₄/T₁ ratio to 0.9 (mean ± SD)

a) As minor protocol violations, subjects who did not recover to a T₄/T₁ ratio of 0.9 within 90 minutes after sugammadex administration and received neostigmine and subjects whose neuromuscular blockade was not measured appropriately by a neuromuscular monitor were excluded.

b) Subjects with missing times to recovery of the T₄/T₁ ratio to 0.9 were excluded.

The number of subjects with adverse events (including laboratory test abnormalities) or adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied during the trial period (from the day of surgery to 7 days after surgery) was as shown in the following table. No deaths occurred during the trial period and other serious adverse events were intrauterine infection in 1 Japanese subject in the rocuronium-2.0 mg/kg

group, swollen tongue and glossodynia in 1 Japanese subject in the vecuronium-0.5 mg/kg group, colon injury, procedural complication, and pulmonary embolism in 1 Caucasian subject in the rocuronium-2.0 mg/kg group,⁵³⁾ and bladder tamponade and urinary bladder haemorrhage in 1 Caucasian subject in the vecuronium-0.5 mg/kg group, but a causal relationship to study drug was denied for all events.

Table. Number of subjects with adverse events (A) or adverse events for which a causal relationship to study drug could not be denied (S) in phase II bridging study for reversal of shallow neuromuscular blockade (at the reappearance of T₂) (5.3.5.1.8, Trial 19.4.208)

		Placebo group			Sugammadex groups											
					0.5 mg/kg			1.0 mg/kg			2.0 mg/kg			4.0 mg/kg		
		n	A	S	n	A	S	n	A	S	n	A	S	n	A	S
Japanese	Rocuronium	10	10	0	10	10	1	10	10	0	10	9	2	9	8	1
	Vecuronium	10	10	0	10	9	0	10	9	0	9	9	0	10	9	0
Caucasian	Rocuronium	10	9	3	10	10	1	9	6	2	10	10	2	10	10	1
	Vecuronium	10	8	0	10	10	2	10	6	2	10	9	1	9	7	0

n: Number of subjects included in safety analyses, A: Number of subjects with adverse events, S: Number of subjects with adverse events for which a causal relationship to study drug could not be denied

The main adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied were blood bilirubin increased (1 Japanese subject in the rocuronium-2.0 mg/kg group, 1 Caucasian subject each in the rocuronium-placebo and rocuronium-1.0 mg/kg groups), β₂ microglobulin urine increased (1 Japanese subject in the rocuronium-0.5 mg/kg group, 1 Caucasian subject each in the rocuronium-placebo and vecuronium-1.0 mg/kg groups), etc.

With respect to vital signs (blood pressure and pulse rate), 17 subjects (8 Japanese subjects, 9 Caucasian subjects) had abnormally high systolic or diastolic blood pressure, 14 subjects (5 Japanese subjects, 9 Caucasian subjects) had abnormally low systolic or diastolic blood pressure, 3 subjects (2 Japanese subjects, 1 Caucasian subject) had increased pulse rate, and 1 subject (Japanese subject) had decreased pulse rate, but there were no dose-dependent changes. Adverse events related to these abnormal changes in vital signs occurred in only 4 subjects (procedural hypertension in 1 Japanese subject [the rocuronium-1.0 mg/kg group], hypertension in 2 Caucasian subjects [the rocuronium-4.0 mg/kg and rocuronium-1.0 mg/kg groups], procedural hypotension in 1 Caucasian subject [the rocuronium-4.0 mg/kg group]).

Laboratory adverse events occurred in 44 subjects (15 Japanese subjects, 29 Caucasian subjects) and the main adverse events were β₂ microglobulin urine increased (1 Japanese subject each in the rocuronium-0.5 mg/kg and rocuronium-1.0 mg/kg groups, 1 Caucasian subject each in the rocuronium-placebo, rocuronium-0.5 mg/kg, rocuronium-4.0 mg/kg, vecuronium-0.5 mg/kg,

⁵³⁾ This subject died due to pulmonary embolism 16 days after surgery, which was not recorded as a death, as the trial period ended 7 days after surgery.

vecuronium-1.0 mg/kg, and vecuronium-4.0 mg/kg groups).

Based on the above, the applicant explained that a dose response of sugammadex administered at the reappearance of T₂ for reversal of rocuronium- or vecuronium-induced neuromuscular blockade and its similarity between Japanese and Caucasian subjects were demonstrated and there were also no relevant differences in safety between Japanese and Caucasian subjects.

4.(ii).A.(2).2 Bridging study for reversal of profound neuromuscular blockade (at 1-2 PTCs) (5.3.5.1.9, Trial 19.4.209 [October 2005 to August 2006])

A randomized, parallel-group, open-label comparative trial was conducted to assess the efficacy and safety of sugammadex in the reversal of profound rocuronium- or vecuronium-induced neuromuscular blockade (at 1-2 PTCs⁴⁴⁾) in Japanese and Caucasian patients with ASA Class 1-3 scheduled for surgical procedures in the supine position under sevoflurane anesthesia with an anticipated duration of about 1.5 to 3 hours (Target sample size of 200, 100 Japanese subjects and 100 Caucasian subjects, 10 subjects per group).⁵⁴⁾

Sugammadex (0.5, 1.0, 2.0, 4.0, 8.0 mg/kg) was to be intravenously administered as a single bolus dose at 1-2 PTCs. For neuromuscular blockade, an intubating dose of 0.9 mg/kg rocuronium or 0.1 mg/kg vecuronium with maintenance doses of 0.1 to 0.2 mg/kg rocuronium or 0.02 to 0.04 mg/kg vecuronium as required (the maintenance doses of vecuronium were 0.02-0.03 mg/kg⁴¹⁾ for Caucasian subjects) was to be administered intravenously. Propofol was used for induction of anesthesia and anesthesia was maintained with sevoflurane and an opioid analgesic and nitrous oxide, if necessary.

A total of 200 subjects were treated and included in safety analyses. Of whom, 188 subjects were included in the PPS for efficacy analyses. Excluded were 12 subjects with serious protocol violations⁵⁵⁾ (7 subjects with violations as to the dose of sugammadex, 2 subjects with violations as to the timing of sugammadex administration, 1 subject with a violation as to concomitant medications, 1 subject with a violation as to the exclusion criteria, 1 subject with all PTC data missing). The number of subjects analyzed of each group was as shown in the following table. Of the PPS, 6 subjects with minor protocol violations (subjects whose neuromuscular blockade was not measured appropriately by a neuromuscular monitor) were excluded from the analysis of the primary efficacy endpoint.

⁵⁴⁾ As Trial 19.4.209, Trial 19.4.209A in Japanese subjects and Trial 19.4.209B in Caucasian subjects were conducted using the identical protocol.

⁵⁵⁾ The volume of the drug solution to be administered, rounded to the first decimal place, was mistakenly indicated by the registration center, which resulted in "violations as to the dose of sugammadex." One subject with all PTC data missing received sugammadex and rocuronium at the same time due to a drug-administration error.

Table. Numbers of subjects included in safety analysis population and PPS of each group in phase II bridging study for reversal of profound neuromuscular blockade (at 1-2 PTCs) (5.3.5.1.9, Trial 19.4.209)

Race	Neuromuscular blocking agent	Analysis population	Sugammadex groups					Total
			0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	4.0 mg/kg	8.0 mg/kg	
Japanese	Rocuronium	Safety	9	9	10	11	10	49
		PPS	6	9	10	11	10	46
	Vecuronium	Safety	10	10	10	10	10	50
		PPS	7	10	10	10	10	47
Caucasian	Rocuronium	Safety	9	10	10	11	10	50
		PPS	8	10	10	10	10	48
	Vecuronium	Safety	9	10	11	10	11	51
		PPS	8	9	11	9	10	47

The primary endpoint of the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio¹⁴⁾ to 0.9 in the PPS was as shown in the following table.

Table. Time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9 (min:sec) (PPS) in phase II bridging study for reversal of profound neuromuscular blockade (at 1-2 PTCs) (5.3.5.1.9, Trial 19.4.209)

			Sugammadex groups					
			0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	4.0 mg/kg	8.0 mg/kg	
Japanese	Rocuronium	N	PPS	6	9	10	11	10
			Minor violation ^{a)}	0	2	0	0	0
			Missing data ^{b)}	0	0	0	0	0
			Evaluated	6	7	10	11	10
		Recovery time (min:sec)	66:54 ± 34:38	4:44 ± 1:44	3:26 ± 2:31	1:35 ± 0:53	1:19 ± 0:34	
	Vecuronium	N	PPS	7	10	10	10	10
			Minor violation ^{a)}	1	2	0	0	0
			Missing data ^{b)}	1	1	0	0	0
			Evaluated	5	7	10	10	10
		Recovery time (min:sec)	79:29 ± 46:14	39:49 ± 45:46	16:01 ± 42:12	3:03 ± 2:23	2:56 ± 3:46	
Caucasian	Rocuronium	N	PPS	8	10	10	10	10
			Minor violation ^{a)}	0	0	0	0	0
			Missing data ^{b)}	0	1	0	0	0
			Evaluated	8	9	10	10	10
		Recovery time (min:sec)	79:47 ± 33:01	28:00 ± 43:44	3:10 ± 1:31	1:39 ± 0:39	1:08 ± 0:20	
	Vecuronium	N	PPS	8	9	11	9	10
			Minor violation ^{a)}	0	0	0	1	0
			Missing data ^{b)}	1	0	0	0	0
			Evaluated	7	9	11	8	10
		Recovery time (min:sec)	68:24 ± 31:56	25:07 ± 24:52	9:05 ± 20:33	3:18 ± 3:27	1:39 ± 0:45	

Recovery time: Time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9 (mean ± SD)

a) As minor protocol violations, subjects whose neuromuscular blockade was not measured appropriately by a neuromuscular monitor were excluded.

b) Subjects with missing times to recovery of the T_4/T_1 ratio to 0.9 were excluded.

The number of subjects with adverse events (including laboratory test abnormalities) or adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied during the trial period (from the day of surgery to 7 days after surgery) was as shown in the following table. No deaths occurred and other serious adverse events were

retinal detachment in 1 Japanese subject in the rocuronium-1.0 mg/kg group, epistaxis in 1 Japanese subject in the vecuronium-2.0 mg/kg group, disseminated intravascular coagulation in 1 Japanese subject in the vecuronium-4.0 mg/kg group, wound haemorrhage in 1 Caucasian subject in the rocuronium-0.5 mg/kg group, tracheal stenosis and laryngeal oedema in 1 Caucasian subject in the rocuronium-2.0 mg/kg group, convulsion, hypoxia, and meningitis in 1 Caucasian subject in the rocuronium-4.0 mg/kg group, and post procedural haemorrhage in 1 Caucasian subject in the vecuronium-8.0 mg/kg group, but a causal relationship to study drug was denied for all events.

Table. Number of subjects with adverse events (A) or adverse events for which a causal relationship to study drug could not be denied (S) in phase II bridging study for reversal of profound neuromuscular blockade (at 1-2 PTCs) (5.3.5.1.9, Trial 19.4.209)

		Sugammadex groups														
		0.5 mg/kg			1.0 mg/kg			2.0 mg/kg			4.0 mg/kg			8.0 mg/kg		
		n	A	S	n	A	S	n	A	S	n	A	S	n	A	S
Japanese	Rocuronium	9	9	0	9	9	0	10	10	2	11	11	1	10	10	1
	Vecuronium	10	10	2	10	9	2	10	10	0	10	9	1	10	10	1
Caucasian	Rocuronium	9	6	2	10	8	4	10	8	2	11	10	3	10	8	3
	Vecuronium	9	6	2	10	6	2	11	7	1	10	6	3	11	8	1

n: Number of subjects included in safety analyses, A: Number of subjects with adverse events, S: Number of subjects with adverse events for which a causal relationship to study drug could not be denied

The main adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied were thirst (1 Japanese subject each in the rocuronium-4.0 mg/kg, rocuronium-8.0 mg/kg, vecuronium-0.5 mg/kg, vecuronium-1.0 mg/kg, vecuronium-4.0 mg/kg, and vecuronium-8.0 mg/kg groups), nausea (2 Caucasian subjects in the rocuronium-0.5 mg/kg group, 3 Caucasian subjects in the rocuronium-1.0 mg/kg group, 1 Caucasian subject in the rocuronium-2.0 mg/kg group, 1 Caucasian subject in the rocuronium-4.0 mg/kg group, 1 Caucasian subject in the rocuronium-8.0 mg/kg group, 1 Caucasian subject in the vecuronium-0.5 mg/kg group, 2 Caucasian subjects in the vecuronium-4.0 mg/kg group), procedural complication (1 Japanese subject in the rocuronium-2.0 mg/kg group, 1 Caucasian subject each in the rocuronium-2.0 mg/kg and rocuronium-8.0 mg/kg groups), etc.

With respect to vital signs (blood pressure and pulse rate), 8 subjects (all Japanese subjects) had abnormally high systolic or diastolic blood pressure, 14 subjects (5 Japanese subjects, 9 Caucasian subjects) had abnormally low systolic or diastolic blood pressure, 1 subject (Japanese subject) had increased pulse rate, and 2 subjects (both Caucasian subjects) had decreased pulse rate, but there were no dose-dependent changes. Adverse events related to these abnormal changes in vital signs occurred in 2 subjects only (procedural hypertension in 1 Japanese subject [the rocuronium-8.0 mg/kg group], procedural hypotension in 1 Caucasian subject [the vecuronium-8.0 mg/kg group]).

Laboratory adverse events occurred in 19 subjects (11 Japanese subjects, 8 Caucasian subjects) and the main adverse events were anaemia (1 Japanese subject each in the rocuronium-1.0 mg/kg, rocuronium-4.0 mg/kg, and rocuronium-8.0 mg/kg groups, 1 Caucasian subject in the vecuronium-2.0 mg/kg group), β_2 microglobulin urine increased (1 Japanese subject each in the rocuronium-0.5 mg/kg, vecuronium-0.5 mg/kg, and vecuronium-4.0 mg/kg groups), β_2 microglobulin increased (1 Japanese subject in the rocuronium-0.5 mg/kg group, 1 Caucasian subject each in the rocuronium-0.5 mg/kg and vecuronium-2.0 mg/kg groups), etc.

Based on the above, the applicant explained that a dose response of sugammadex administered at 1-2 PTCs for reversal of rocuronium- or vecuronium-induced neuromuscular blockade and its similarity between Japanese and Caucasian subjects were demonstrated and there were also no relevant differences in safety between Japanese and Caucasian subjects.

4.(ii).A.(3) Foreign phase III trials

4.(ii).A.(3).1) Neostigmine-controlled comparative trial for reversal of shallow neuromuscular blockade (at the reappearance of T₂) (5.3.5.1.13, Trial 19.4.301 [November 2005 to March 2006])

A neostigmine-controlled, randomized, parallel-group, safety-assessor blinded, comparative trial was conducted to assess the efficacy and safety of sugammadex in the reversal of shallow rocuronium- or vecuronium-induced neuromuscular blockade (at the reappearance of T₂) in foreign patients with ASA Class 1-4 scheduled for surgical procedures in the supine position (Target sample size of 196, 49 subjects per group).

A bolus dose of 2.0 mg/kg sugammadex or 50 μ g/kg neostigmine⁵⁶⁾ was to be administered intravenously at the reappearance of T₂.⁴²⁾ For neuromuscular blockade, an intubating dose of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium with maintenance doses of 0.1 to 0.2 mg/kg rocuronium or 0.02 to 0.03 mg/kg vecuronium as required was to be administered intravenously. Propofol was used for induction of anesthesia and anesthesia was maintained with sevoflurane and an opioid analgesic.

A total of 189 subjects were treated (48 subjects in the rocuronium-sugammadex group, 48 subjects in the rocuronium-neostigmine group, 48 subjects in the vecuronium-sugammadex group, 45 subjects in the vecuronium-neostigmine group), all of whom were included in the Intention-to-treat (ITT) population and analyzed for safety and efficacy.

⁵⁶⁾ A muscarinic cholinergic receptor antagonist, glycopyrrolate (unapproved in Japan) and neostigmine are premixed at a mass ratio of 1:5.

The primary endpoint of the geometric mean time from start of administration of sugammadex or neostigmine to recovery of the T_4/T_1 ratio¹⁴⁾ to 0.9 in the ITT population (including imputed data,⁴⁸⁾ Min.-Max.) was 1 minute: 29 seconds (55 seconds - 5 minutes: 25 seconds) in the rocuronium-sugammadex group, 18 minutes: 30 seconds (3 minutes: 40 seconds - 106 minutes: 53 seconds) in the rocuronium-neostigmine group, 2 minutes: 48 seconds (1 minute: 12 seconds - 64 minutes: 12 seconds) in the vecuronium-sugammadex group, and 16 minutes: 48 seconds (2 minutes: 55 seconds - 76 minutes: 9 seconds) in the vecuronium-neostigmine group, demonstrating a statistically significant difference between the rocuronium-sugammadex group and the rocuronium-neostigmine group and between the vecuronium-sugammadex group and vecuronium-neostigmine group ($P < 0.0001$, a 2-way ANOVA on log transformed times to recovery, including treatment group and center as factors).

Adverse events (including laboratory test abnormalities) occurred in 85.4% of the rocuronium-sugammadex group (41 of 48 subjects), 89.6% of the rocuronium-neostigmine group (43 of 48 subjects), 70.8% of the vecuronium-sugammadex group (34 of 48 subjects), and 80.0% of the vecuronium-neostigmine group (36 of 45 subjects). No deaths occurred and other serious adverse events were post procedural haemorrhage (2 subjects) in the rocuronium-sugammadex group and postoperative infection and procedural complication (1 subject), peripheral ischaemia and peripheral arterial occlusive disease (1 subject), and subileus (1 subject) in the rocuronium-neostigmine group, but a causal relationship to study drug was denied for all events.

Adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied occurred in 14.6% of the rocuronium-sugammadex group (7 of 48 subjects), 20.8% of the rocuronium-neostigmine group (10 of 48 subjects), 14.6% of the vecuronium-sugammadex group (7 of 48 subjects), and 22.2% of the vecuronium-neostigmine group (10 of 45 subjects) and the main events were dry mouth (3 subjects in the rocuronium-sugammadex group, 3 subjects in the rocuronium-neostigmine group, 4 subjects in the vecuronium-neostigmine group), nausea (2 subjects in the rocuronium-sugammadex group, 2 subjects in the rocuronium-neostigmine group, 2 subjects in the vecuronium-sugammadex group, 2 subjects in the vecuronium-neostigmine group), procedural hypertension (2 subjects in the rocuronium-sugammadex group, 2 subjects in the vecuronium-sugammadex group, 1 subject in the vecuronium-neostigmine group), vomiting (2 subjects in the rocuronium-sugammadex group, 2 subjects in the vecuronium-sugammadex group), procedural complication (4 subjects in the vecuronium-neostigmine group), etc.

With respect to vital signs (blood pressure and pulse rate), 8 subjects treated with sugammadex and 10 subjects treated with neostigmine had abnormally high systolic or diastolic blood pressure, 8 subjects treated with sugammadex and 4 subjects treated with neostigmine had abnormally low systolic or diastolic blood pressure, and 5 subjects treated with neostigmine had decreased pulse rate. Adverse events related to these abnormal changes in vital signs were procedural hypertension (2 subjects in the vecuronium-sugammadex group, 2 subjects in the vecuronium-neostigmine group) and procedural hypotension (1 subject in the rocuronium-sugammadex group, 1 subject in the rocuronium-neostigmine group). There were no clinically relevant changes in ECGs.

Laboratory adverse events occurred in 10 subjects treated with sugammadex and 12 subjects treated with neostigmine and the main events were γ -GPT increased (1 subject in the rocuronium-sugammadex group, 1 subject in the vecuronium-sugammadex group, 2 subjects in the vecuronium-neostigmine group), ALT increased (1 subject in the rocuronium-sugammadex group, 2 subjects in the vecuronium-sugammadex group, 1 subject in the vecuronium-neostigmine group), albumin urine present (1 subject in the rocuronium-sugammadex group, 2 subjects in the rocuronium-neostigmine group, 1 subject in the vecuronium-sugammadex group), etc.

Based on the above, the applicant explained that 2.0 mg/kg sugammadex was shown to be superior to 50 μ g/kg neostigmine as a reversal agent of a neuromuscular blockade induced by rocuronium or vecuronium at the reappearance of T₂ and there were no particular safety problems.

4.(ii).A.(3).2) Neostigmine-controlled comparative trial for reversal of profound neuromuscular blockade (at 1-2 PTCs) (5.3.5.1.15, Trial 19.4.302 [November 2005 to November 2006])

A neostigmine-controlled, randomized, parallel-group, safety-assessor blinded, comparative trial was conducted to assess the efficacy and safety of sugammadex in the reversal of profound rocuronium- or vecuronium-induced neuromuscular blockade (at 1-2 PTCs) in foreign patients with ASA Class 1-4 scheduled for surgical procedures in the supine position (Target sample size

of 144, 36 subjects per group⁵⁷⁾).

A bolus dose of 4.0 mg/kg sugammadex or 70 µg/kg neostigmine⁵⁶⁾ was to be administered intravenously at 1-2 PTCs. For neuromuscular blockade, an intubating dose of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium with maintenance doses of 0.15 mg/kg rocuronium or 0.015 mg/kg vecuronium as required was to be administered intravenously. Propofol was used for induction of anesthesia and anesthesia was maintained with sevoflurane and an opioid analgesic.

A total of 157 subjects were treated (37 subjects in the rocuronium-sugammadex group, 37 subjects in the rocuronium-neostigmine group, 47 subjects in the vecuronium-sugammadex group,⁵⁸⁾ 36 subjects in the vecuronium-neostigmine group), all of whom were included in the ITT population and analyzed for safety and efficacy.

The primary endpoint of the geometric mean time from start of administration of sugammadex or neostigmine to recovery of the T_4/T_1 ratio¹⁴⁾ to 0.9 in the ITT population (including imputed data,⁴⁸⁾ Min.-Max.) was 2 minutes: 52 seconds (1 minute: 13 seconds - 16 minutes: 5 seconds) in the rocuronium-sugammadex group, 50 minutes: 22 seconds (13 minutes: 16 seconds - 145 minutes: 40 seconds) in the rocuronium-neostigmine group, 4 minutes: 28 seconds (1 minute: 26 seconds - 68 minutes: 25 seconds) in the vecuronium-sugammadex group, and 66 minutes: 12 seconds (46 minutes: 1 second - 312 minutes: 39 seconds) in the vecuronium-neostigmine group, demonstrating a statistically significant difference between the rocuronium-sugammadex group and the rocuronium-neostigmine group and between the vecuronium-sugammadex group and the vecuronium-neostigmine group ($P < 0.0001$, a 2-way ANOVA on log transformed times to recovery, including treatment group and center as factors).

Adverse events (including laboratory test abnormalities) occurred in 97.3% of the rocuronium-sugammadex group (36 of 37 subjects), 97.4% of the rocuronium-neostigmine group (37 of 38 subjects), 100.0% of the vecuronium-sugammadex group (46 of 46 subjects), and 91.7% of the vecuronium-neostigmine group (33 of 36 subjects). No deaths occurred and

⁵⁷⁾In Trial 19.4.302 (5.3.5.1.15), the 1st interim analysis was planned for early stopping due to efficacy when data from 10 subjects in each group were collected. The level of significance for the interim analysis was adjusted using the method of Hwang, Shih and De Cani and the level of significance for pairwise comparisons was calculated to be 0.0025 (one-sided) for the interim analysis and 0.02335 (one-sided) for the final analysis. The interim analysis demonstrated a statistically significant difference between the rocuronium-sugammadex group and the rocuronium-neostigmine group (active control) and between the vecuronium-sugammadex group and the vecuronium-neostigmine group (active control) ($P < 0.0001$, a 2-way ANOVA on log transformed times to recovery, including treatment group and center as factors) and the Data and Safety Monitoring Board (DSMB) recommended stopping enrollment in the active control groups, but as the target sample size had already been achieved by that time, the target sample size remained unchanged.

⁵⁸⁾Since 1 subject in the vecuronium-sugammadex group mistakenly received rocuronium-neostigmine, this subject was treated as a rocuronium-neostigmine group subject for safety analyses.

other serious adverse events were postoperative infection (1 subject) and postoperative ileus (1 subject) in the rocuronium-sugammadex group, nausea, pain, and dyspnoea (1 subject) and postoperative ileus (1 subject) in the rocuronium-neostigmine group, and atelectasis (1 subject) and splenic abscess (1 subject) in the vecuronium-sugammadex group and a causal relationship to study drug was denied for all events. Adverse events leading to discontinuation were reported by 1 subject in the rocuronium-neostigmine group (gastric perforation and procedural complication), but their causal relationship to study drug was denied.

Adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied occurred in 27.0% of the rocuronium-sugammadex group (10 of 37 subjects), 31.6% of the rocuronium-neostigmine group (12 of 38 subjects), 19.6% of the vecuronium-sugammadex group (9 of 46 subjects), and 27.8% of the vecuronium-neostigmine group (10 of 36 subjects). The main events were nausea (2 subjects in the rocuronium-sugammadex group, 5 subjects in the rocuronium-neostigmine group, 3 subjects in the vecuronium-sugammadex group, 2 subjects in the vecuronium-neostigmine group), post procedural nausea (2 subjects in the rocuronium-sugammadex group, 2 subjects in the rocuronium-neostigmine group, 2 subjects in the vecuronium-sugammadex group, 1 subject in the vecuronium-neostigmine group), muscular weakness (3 subjects in the rocuronium-sugammadex group, 3 subjects in the rocuronium-neostigmine group), vomiting (2 subjects in the rocuronium-sugammadex group, 2 subjects in the rocuronium-neostigmine group), etc.

With respect to vital signs (blood pressure and pulse rate), 8 subjects treated with sugammadex and 6 subjects treated with neostigmine had abnormally high systolic or diastolic blood pressure, 7 subjects treated with sugammadex and 6 subjects treated with neostigmine had abnormally low systolic or diastolic blood pressure, 1 subject treated with sugammadex and 2 subjects treated with neostigmine had increased pulse rate, and 1 subject treated with neostigmine had decreased pulse rate. Adverse events related to these abnormal changes in vital signs were procedural hypertension (1 subject in the rocuronium-sugammadex group, 1 subject in the vecuronium-neostigmine group), procedural hypotension (1 subject in the rocuronium-neostigmine group), and diastolic/systolic blood pressure increased (1 subject in the vecuronium-sugammadex group).

Laboratory adverse events occurred in 17 subjects treated with sugammadex and 17 subjects treated with neostigmine and the main events were anaemia (1 subject in the rocuronium-sugammadex group, 3 subjects in the rocuronium-neostigmine group, 1 subject in

the vecuronium-neostigmine group), postoperative anaemia (2 subjects in the rocuronium-sugammadex group, 2 subjects in the rocuronium-neostigmine group, 1 subject in the vecuronium-neostigmine group), leukocytosis (1 subject in the rocuronium-sugammadex group, 1 subject in the rocuronium-neostigmine group, 1 subject in the vecuronium-sugammadex group, 2 subjects in the vecuronium-neostigmine group), etc.

Based on the above, the applicant explained that significantly faster recovery from a neuromuscular blockade induced by rocuronium or vecuronium after reversal at 1-2 PTCs by 4.0 mg/kg sugammadex compared to 70 µg/kg neostigmine was demonstrated and there were no particular safety problems.

4.(ii).A.(3).3) Suxamethonium-controlled, comparative trial in an immediate reversal setting (5.3.5.1.16, Trial 19.4.303 [February 2006 to August 2006])

A suxamethonium-controlled, randomized, parallel-group, safety assessor-blinded, comparative trial was conducted to assess the efficacy and safety of sugammadex administered at 3 minutes after rocuronium administration in the reversal of rocuronium-induced neuromuscular blockade in foreign patients with ASA Class 1 or 2 scheduled for surgical procedures in the supine position (Target sample size of 110, 55 subjects per group).

Subjects in the sugammadex group were to intravenously receive a bolus dose of 16.0 mg/kg sugammadex at 3 minutes following a bolus intubating dose of 1.2 mg/kg rocuronium. Subjects in the suxamethonium group were to receive a bolus dose of 1.0 mg/kg suxamethonium intravenously. Propofol, an opioid analgesic, and drugs needed in clinical practice such as an inhaled anesthetic were used for induction and maintenance of anesthesia.

A total of 110 subjects were treated (55 subjects in the sugammadex group, 55 subjects in the suxamethonium group⁵⁹⁾), all of whom were included in the ITT population and analyzed for safety and efficacy.

⁵⁹⁾ One subject who was randomized to sugammadex but mistakenly received suxamethonium and 2 subjects who were randomized to suxamethonium but mistakenly received sugammadex were analyzed for safety based on the actual treatment received.

The primary endpoint of the time from start of administration of a neuromuscular blocking agent (rocuronium [sugammadex group] or suxamethonium) to recovery of T_1 to 10%^{60), 61)} (recovery time to a T_1 of 10%, mean \pm SD) in the ITT population was 4 minutes: 22 seconds \pm 44 seconds in the sugammadex group and 7 minutes: 4 seconds \pm 1 minute: 34 seconds in the suxamethonium group, demonstrating a statistically significant difference between the two groups (including imputed data,⁴⁸⁾ $P < 0.0001$, a 2-way ANOVA including treatment group and center as factors).

Adverse events (including laboratory test abnormalities) occurred in 92.9% of the sugammadex group (52 of 56 subjects) and 94.4% of the suxamethonium group (51 of 54 subjects). No deaths occurred and other serious adverse event was reported by 1 subject in the suxamethonium group (pelvic haematoma), but its causal relationship to study drug was denied.

Adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied occurred in 14.3% of the sugammadex group (8 of 56 subjects) and 14.8% of the suxamethonium group (8 of 54 subjects) and the main events were procedural complication (4 subjects in the sugammadex group), procedural hypertension (2 subjects in the sugammadex group, 2 subjects in the suxamethonium group), nausea (2 subjects in the sugammadex group, 1 subject in the suxamethonium group), etc.

With respect to vital signs (blood pressure and pulse rate), 7 subjects in the sugammadex group and 8 subjects in the suxamethonium group had abnormally high systolic or diastolic blood pressure, 21 subjects in the sugammadex group and 11 subjects in the suxamethonium group had abnormally low systolic or diastolic blood pressure, 2 subjects in the sugammadex group and 1 subject in the suxamethonium group had decreased pulse rate, and 2 subjects in the sugammadex group had increased pulse rate. Adverse events related to these abnormal changes in vital signs were procedural hypotension (5 subjects in the sugammadex group, 7 subjects in the suxamethonium group), procedural hypertension (1 subject in the sugammadex group, 4 subjects in the suxamethonium group), and bradycardia (1 subject in the suxamethonium group).

⁶⁰⁾ Fading (muscle contractions after TOF stimulation using a neuromuscular monitor diminish) is not observed following administration of a depolarizing muscle relaxant suxamethonium. Therefore, in Trial 19.4.303, the time from start of administration of rocuronium or suxamethonium to recovery of first twitch height T_1 to 10% (First time point from a sequence of three time points that the T_1 response is $\geq 10\%$ of the final T_1) was used as the primary endpoint.

⁶¹⁾ Two analyses were performed: one in which missing data were imputed and the other in which only observed data were used. The results of analysis using the imputed data only are presented in this report. The 95th percentile (P95) and the 5th percentile (P5) of the available times to recovery of T_1 to 10% were calculated and P95 or P5 was imputed for a missing recovery time in the sugammadex or suxamethonium group, respectively.

Laboratory adverse events occurred in 12 subjects and the main events were anaemia (3 subjects in the sugammadex group, 3 subjects in the suxamethonium group), blood creatine phosphokinase increased (2 subjects in the sugammadex group, 1 subject in the suxamethonium group), etc.

Based on the above, the applicant explained that significantly faster recovery to a T_1 of 10% in the reversal of 1.2mg/kg rocuronium-induced neuromuscular blockade with 16.0mg/kg sugammadex administered 3 minutes after rocuronium administration compared to spontaneous recovery after 1.0 mg/kg suxamethonium-induced neuromuscular blockade was demonstrated and there were no particular safety problems with 16.0 mg/kg sugammadex.

4.(ii).A.(3).4) Comparative trial under maintenance anesthesia with sevoflurane or propofol (5.3.5.1.11, Trial 19.4.312 [December 2006 to March 2007])

A randomized, parallel-group, safety assessor-blinded, comparative trial was conducted to assess the efficacy, safety, and pharmacokinetics of sugammadex under maintenance anesthesia with sevoflurane or propofol in foreign patients with ASA Class 1 to 3 scheduled for surgical procedures in the supine position with an anticipated duration of 2 to 5 hours (Target sample size of 50, 25 subjects per group) [for pharmacokinetics, see “4.(i) Summary of human pharmacokinetic and pharmacodynamic trials”].

A bolus dose of 4.0 mg/kg sugammadex was to be intravenously administered at a T_1 of 3% to 10% after rocuronium continuous infusion. Propofol was used for induction of anesthesia and anesthesia was maintained with sevoflurane or propofol⁶²⁾ and an opioid analgesic. For neuromuscular blockade, the intravenous bolus administration of rocuronium (an intubating dose of 0.6 mg/kg) was followed by continuous infusion of rocuronium for maintenance, starting with an infusion rate of 7 μ g/kg/min with subsequent adjustment by titration to maintain a depth of neuromuscular blockade of zero responses to TOF and PTC of ≤ 10 responses for ≥ 90 minutes.

A total of 51 subjects were treated (26 subjects in the sevoflurane group, 25 subjects in the propofol group), all of whom were included in the ITT population and analyzed for safety and efficacy.

The primary endpoint of the median time from start of administration of sugammadex to

⁶²⁾ Maintenance of anesthesia was done in accordance with the dosage and dose regimen used in routine clinical practice and the end-tidal sevoflurane concentration was maintained at 1.5 vol %.

recovery of the T_4/T_1 ratio¹⁴⁾ to 0.9 (Min.-Max.) in the ITT population was 1 minute: 20 seconds (38 seconds - 2 minutes: 25 seconds) in the sevoflurane group and 1 minute: 11 seconds (44 seconds - 2 minutes: 26 seconds) in the propofol group. The estimated treatment difference in recovery time was 9 seconds with a corresponding 95% confidence interval (CI) ranging from -6 seconds to +20 seconds (Hodges-Lehman estimate) and since the 95% CI lied within the pre-defined equivalence interval, which ranged from -60 to +60 seconds, equivalence of effects of sugammadex under maintenance anesthesia with sevoflurane and propofol was demonstrated.

Adverse events (including laboratory test abnormalities) occurred in 92.3% of the sevoflurane group (24 of 26 subjects) and 88.0% of the propofol group (22 of 25 subjects), but there were no deaths or other serious adverse events.

As adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be denied, only procedural hypotension was reported by 1 subject in the sevoflurane group.

With respect to vital signs (blood pressure and pulse rate), 5 subjects in the sevoflurane group had abnormally high systolic or diastolic blood pressure and 2 subjects in the sevoflurane group had abnormally low systolic or diastolic blood pressure. Adverse events related to these abnormal changes in vital signs were hypertension in 1 subject and procedural hypotension in 1 subject (both in the sevoflurane group).

Laboratory adverse events occurred in 3 subjects in the sevoflurane group and 3 subjects in the propofol group, and the main events were hypokalaemia (1 subject in the sevoflurane group, 2 subjects in the propofol group).

Based on the above, the applicant explained that there are no major differences in the efficacy and safety of sugammadex between sevoflurane and propofol anesthesia.

In addition, the applicant explained as follows:

In a foreign phase II, comparative trial under sevoflurane or propofol anesthesia (5.3.5.1.10, Trial 19.4.210 [December 2003 to March 2004]), there were no major differences in the efficacy and safety of 2.0 mg/kg sugammadex when administered at the reappearance of T_2 after rocuronium administration between subjects who received sevoflurane and subjects who received propofol for maintenance of anesthesia. In a dose-finding trial of 0.5 to 4.0 mg/kg of sugammadex administered at the reappearance of T_2 after rocuronium, vecuronium, and

pancuronium administration (5.3.5.1.7, Trial 19.4.207 [March 2003 to September 2004]), no dose-response relationship of sugammadex in reversing a pancuronium-induced neuromuscular blockade was observed. The efficacy of sugammadex was confirmed and there were no particular safety problems in the following foreign phase III trials where 2.0 or 4.0 mg/kg (0.5 or 1 mg/kg in the pediatric trial) of sugammadex was administered at the reappearance of T₂: (a) a trial in patients with renal impairment (5.3.5.1.17, Trial 19.4.304); (b) a trial in geriatric subjects (5.3.5.1.18, Trial 19.4.305); (c) a placebo-controlled comparative trial in pediatric patients (5.3.5.1.12, Trial 19.4.306); (d) a placebo-controlled comparative trial in patients with pulmonary complications (5.3.5.1.19, Trial 19.4.308); (e) a placebo-controlled comparative trial in patients with a cardiac disease (5.3.5.1.20, Trial 19.4.309); and (f) a cisatracurium (unapproved in Japan)-neostigmine controlled comparative trial of rocuronium-sugammadex (5.3.5.1.14, Trial 19.4.310), and in a phase III trial (5.3.5.2.1, Trial 19.4.311) where 4.0 mg/kg of sugammadex was administered at 15 minutes after the intubating dose of 0.6 mg/kg rocuronium or the last maintenance dose of 0.15 mg/kg rocuronium.

4.(ii).B Outline of the review by PMDA

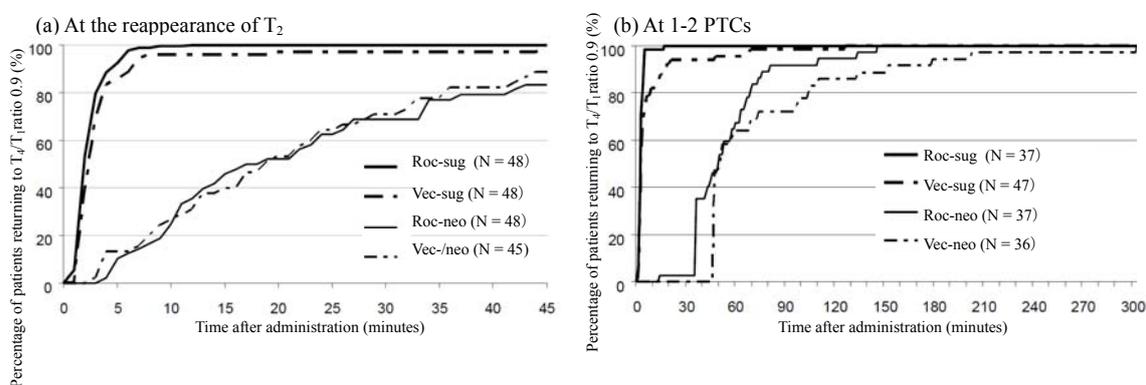
4.(ii).B.(1) Clinical positioning of sugammadex

PMDA asked the applicant to explain the clinical positioning of sugammadex as a neuromuscular blockade reversal agent, compared with an acetylcholinesterase inhibitor, neostigmine.

The applicant explained as follows:

Neostigmine, which is currently available as a neuromuscular blockade reversal agent in Japan, reverses neuromuscular blockade by inhibiting the hydrolysis of acetylcholine and indirectly increasing acetylcholine at the neuromuscular junction. However, neostigmine is ineffective in reversing profound neuromuscular blockade and it is cautioned in the package insert that neostigmine should be administered after recovery on neuromuscular monitoring or the return of spontaneous respiration is confirmed. In addition, neostigmine causes hypotension, bradycardia, arrhythmia, abdominal cramp, bronchoconstriction, salivary gland secretion, vomiting, diarrhoea, etc. due to its interactions with the muscarinic receptor (Morgan GE et al eds. *Clinical Anesthesiology 4th ed.* New York; 2006, Package insert for Neostigmine Methylsulfate Injection, 2005, Suresh D et al. *Anaesthesia.* 1991;46:877-880.). Muscarinic receptor antagonist administered with neostigmine to reduce these side effects also cause a number of side effects, such as tachycardia, thirst, arrhythmia, urinary retention, and vision blurred (Package insert for Atropine Sulfate Injection, 2007, Hardman JG ed. *Goodman and Gilman's Pharmacological Basis of Therapeutics. 10th ed.* New York; 2002, Morgan GE et al

eds. *Clinical Anesthesiology. 4th ed.* New York; 2006:Caption 11.). Sugammadex is a γ -cyclodextrin derivative that does not possess biological activity. In neostigmine-controlled comparative trials (5.3.5.1.13, Trial 19.4.301; 5.3.5.1.15, Trial 19.4.302), the percentages of patients returning to a T_4/T_1 ratio of 0.9 after sugammadex administration were as shown in the following figures, and sugammadex provided faster reversal of both shallow (at the reappearance of T_2) and profound (at 1-2 PTCs) neuromuscular blockade compared with neostigmine. The incidences of the main adverse events (following sugammadex in combination with rocuronium or vecuronium) were as shown in the following table, and there were no major differences between the two groups.



Figures. Time course of percentage of patients returning to a T_4/T_1 ratio of 0.9 following sugammadex (sug) 2.0 mg/kg or neostigmine (neo) 50 μ g/kg at the reappearance of T_2 (left) or following sugammadex 4.0 mg/kg or neostigmine 70 μ g/kg at 1-2 PTCs (right) after rocuronium (Roc)- or vecuronium (Vec)-induced neuromuscular blockade (5.3.5.1.13, Trial 19.4.301; 5.3.1.151, Trial 9.4.302)

Table. Number of subjects with main adverse events following sugammadex in combination with rocuronium or vecuronium in neostigmine-controlled foreign phase III trials (5.3.5.1.13, Trial 19.4.301; 5.3.1.151, Trial 9.4.302) (Incidence %)

	Sugammadex group (N = 179)	Neostigmine group (N = 167)
Any adverse event	157 (87.7)	149 (89.2)
Injury, poisoning and procedural complications	120 (67.0)	113 (67.7)
Procedural pain	98 (54.7)	85 (50.9)
Procedural nausea	14 (7.8)	13 (7.8)
Procedural complication	6 (3.4)	14 (8.4)
Gastrointestinal disorders	84 (46.9)	89 (53.3)
Nausea	63 (35.2)	61 (36.5)
Vomiting	28 (15.6)	22 (13.2)
General disorders and administration site conditions	40 (22.3)	35 (21.0)
Pain	18 (10.1)	14 (8.4)
Nervous system disorders	32 (17.9)	34 (20.4)
Headache	21 (11.7)	13 (7.8)

Furthermore, the applicant explained as follows:

In the clinical situation when, following the administration of an intubating dose of a neuromuscular blocking drug, the clinician is unable to perform endotracheal intubation in an attempt to establish a patent airway, and is also unable to subsequently ventilate the patient via either a face mask or a laryngeal mask airway (cannot intubate - cannot ventilate [CICV]), serious hypoxia may lead to brain injury or death. Although CICV occurs in 0.01% to 0.05% of

attempted intubations (Crosby ET et al. *Can J Anesth.* 1998;45:757-776, Combes X et al, *Anesthesiology*, 2004;100:1146-1150, Benumof JL, *Anesthesiology*, 1991;75:1087-1110.), as an acetylcholinesterase inhibitor can not be used immediately after administration of a neuromuscular blocking drug, non-invasive airway ventilation (supralaryngeal airways, jet ventilation) or invasive airway access (percutaneous tracheostomy, needle cricothyrotomy) is needed. It has been reported that such intubation difficulties were not predicted in 52% of the CICV cases (Paix AD. *Qual Saf Health Care.* 2005;14:e5.). The efficacy and safety of sugammadex in an immediate reversal setting (3 minutes after rocuronium administration) (assuming a CICV situation) have been confirmed and sugammadex resulted in a reduction in the time to recovery of T₁ to 10%⁶⁰⁾ compared to spontaneous recovery from a depolarizing neuromuscular blocking agent suxamethonium, the current drug of choice for rapid sequence intubation (5.3.5.1.16, Trial 19.4.303). As suxamethonium is associated with the risk of arrhythmia, hyperkalaemia, etc. (Miller RD ed. *Miller's Anesthesia.* 2005;481-572, Morgan GE et al eds. *Clinical Anesthesiology 4th ed.* 2006;Capter 11.), the use of sugammadex in combination with rocuronium can reduce complications associated with the neuromuscular blocking agent.

PMDA accepted the above and considers that sugammadex as a neuromuscular blockade reversal agent represents a new option for clinical practice.

4.(ii).B.(2) The ability to extrapolate foreign clinical data

4.(ii).B.(2).1) Criteria for allowing bridging the clinical data between the two regions and comparison of baseline and demographic characteristics between Japan and overseas

Since this application is for sugammadex developed based on the bridging strategy, PMDA asked the applicant to explain the criteria for similarity between Japanese and Caucasian subjects in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) to allow extrapolation of foreign data.

The applicant explained as follows:

The established criteria for determining the similarity between Japanese and Caucasian subjects in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) are: the dose-response curve for the time from start of administration of sugammadex to recovery of the T₄/T₁ ratio to 0.9 is similar visually; a 2-way ANOVA including ethnicity and dose (including the interaction term) as factors is performed on recovery times at doses equal to or higher than the estimated smallest dose and the 95% CI for the point estimate of the difference between Japanese and Caucasian subjects lies within the pre-defined equivalence interval (ranges from -1

minute to 1 minute); and the safety profile (from the day of surgery to the first postoperative day) and the time course of plasma concentration [for the time course of plasma concentration, see “4.(i) Summary of human pharmacokinetic and pharmacodynamic trials”] are similar. The equivalence interval for the time to recovery of the T_4/T_1 ratio to 0.9 (ranges from -1 minute to 1 minute) was defined as values that are generally acceptable as clinically insignificant differences in the recovery time from neuromuscular blockade, referring to the opinions of Japanese and foreign anesthesiologists.

PMDA asked the applicant to explain differences in baseline and demographic characteristics of patients between Japan and overseas in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) and the potential for such differences to affect evaluation.

The applicant explained as follows:

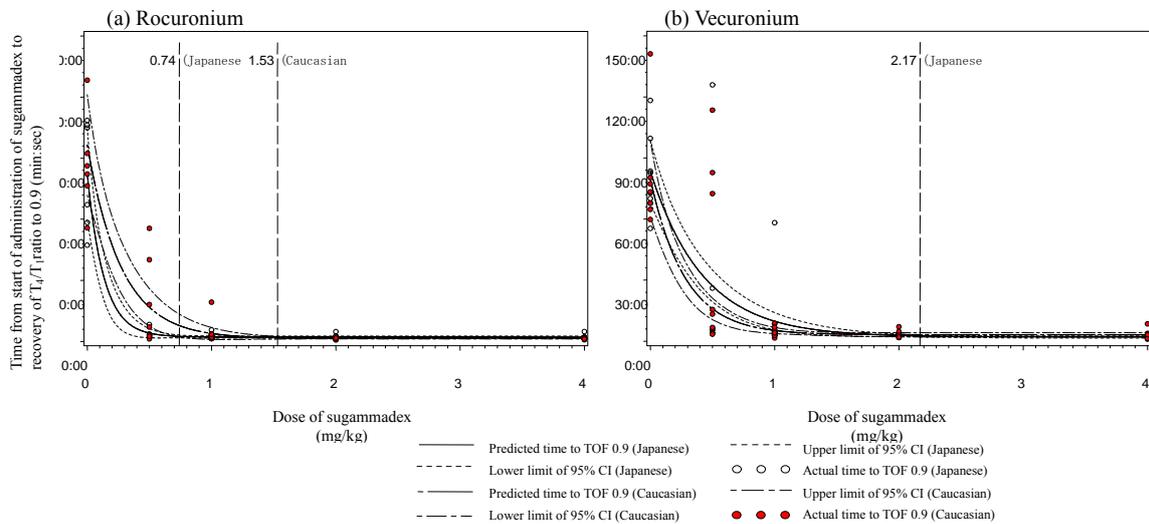
With respect to baseline and demographic characteristics of patients enrolled in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) (age, body weight, height, BMI, gender, ASA Class), body weight and height tended to be lower in Japanese subjects than in Caucasian subjects in both trials and the percentage of subjects classified as ASA Class 1 was higher in Japanese subjects (Japanese, 71%; Caucasian, 45%) and the percentage of females tended to be lower in Japanese subjects (Japanese, 55%; Caucasian, 71%) in Trial 19.4.208 (5.3.5.1.8). Meanwhile, these baseline and demographic characteristics had no effects on the time to recovery of the T_4/T_1 ratio to 0.9 (ANOVA including trial, age category, body weight category, gender, and ASA Class as factors) and there were also no major differences in the incidence of adverse events among the subgroups. As to the types of surgical procedures, the percentage of “ear, nose, and throat” surgeries was higher in Japanese subjects (Japanese, 19%; Caucasian, 1%) and the percentage of “gastrointestinal and pancreatic” surgeries was higher in Caucasian subjects (Japanese, 6%; Caucasian, 30%) in Trial 19.4.208 (5.3.5.1.8), but the types of surgical procedures did not affect the time to recovery of the T_4/T_1 ratio to 0.9 or the incidence of adverse events. Therefore, differences in these baseline and demographic characteristics are unlikely to have affected evaluation.

4.(ii).B.(2).2) Comparison of the time to recovery of the T_4/T_1 ratio to 0.9 between Japanese and Caucasian subjects

PMDA asked the applicant to explain the basis for determining the similarity between Japanese and Caucasian subjects for the primary efficacy endpoint of the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9 in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209).

The applicant explained as follows:

For times from administration of different doses of sugammadex at shallow neuromuscular blockade (at the reappearance of T_2 , 5.3.5.1.8, Trial 19.4.208) to recovery of the T_4/T_1 ratio¹⁴) to 0.9, the dose-response curves assuming an exponential function (Estimated time to recovery of the T_4/T_1 ratio to 0.9 (dose) = $E_0 + b \times e^{-(c \times \text{dose})}$), the coefficients of the dose-response equation, the estimated fastest achievable recovery times, and the estimated smallest doses were as shown in the following figures and table A, which were similar between Japanese and Caucasian subjects. The differences in the time to recovery of the T_4/T_1 ratio to 0.9 between Japanese and Caucasian subjects at doses equal to or higher than the estimated smallest dose were as shown in the following table B. Since the normality of residuals from a 2-way ANOVA model including ethnicity and dose as factors could not be assumed, an additional analysis (nonparametric analysis, Hodges-Lehman estimate) was performed. As a result, the 95% CI for the estimated median difference lied within the equivalence interval (ranged from -1 minute to 1 minute) for rocuronium, but not for vecuronium. However, since the estimated difference was within ± 1 minute, the applicant concluded that there are no major differences in the recovery time from neuromuscular blockade with sugammadex between Japanese and Caucasian subjects for both rocuronium and vecuronium.



Figures. Time from start of administration of 0.5-4 mg/kg sugammadex, administered at the reappearance of T_2 after rocuronium (a) or vecuronium (b) to recovery of the T_4/T_1 ratio to 0.9 (min:sec) in Japanese and Caucasian subjects and the estimated dose-response curve (5.3.5.1.8, Trial 19.4.208, PPS)

Table A. Coefficients of the dose-response equation (an exponential function) for the time from administration of 0.5-4.0 mg/kg of sugammadex at the reappearance of T₂ after rocuronium or vecuronium administration to recovery of the T₄/T₁ ratio to 0.9 in Japanese and Caucasian subjects, the estimated fastest achievable recovery times, and the estimated smallest doses (5.3.5.1.8, Trial 19.4.208, PPS)

		Estimated coefficients of dose-response equation (an exponential function) ^{a)} [95% CI]		Fastest achievable recovery time ^{b)} (E ₀) (min:sec)	Smallest dose ^{c)} (mg/kg)
		b	c		
Japanese	Rocuronium	79.8 [57.2, 102.4]	-7.45 [-9.94, -4.97]	2: 08	0.74
	Vecuronium	81.4 [66.0, 96.9]	-2.36 [-2.94, -1.77]	2: 04	2.17
Caucasian	Rocuronium	95.1 [70.4, 119.7]	-3.66 [-4.91, -2.40]	1: 27	1.53
	Vecuronium	76.0 [25.9, 126.1]	-3.70 [-4.73, -2.66]	3: 13	- ^{d)}

- a) The estimated coefficients of the dose-response equation (an exponential function) “Estimated time to recovery of the T₄/T₁ ratio to 0.9 (dose) = E₀ + b × e^{(-c×dose)¹⁴⁾} (weighted non-linear regression analysis)
b) The estimated fastest achievable time to recovery of the T₄/T₁ ratio to 0.9 (E₀ in the dose-response equation)
c) The dose at which the upper limit of 95% CI of the estimated dose-response curve for the time to recovery of the T₄/T₁ ratio to 0.9 is equal to E₀+1 minutes
d) Although the smallest dose could not be calculated by the initially planned analysis (analysis weighted by variance), the smallest dose was calculated to be 1.47 mg/kg by an additional analysis (analysis weighted by the third power of SD).

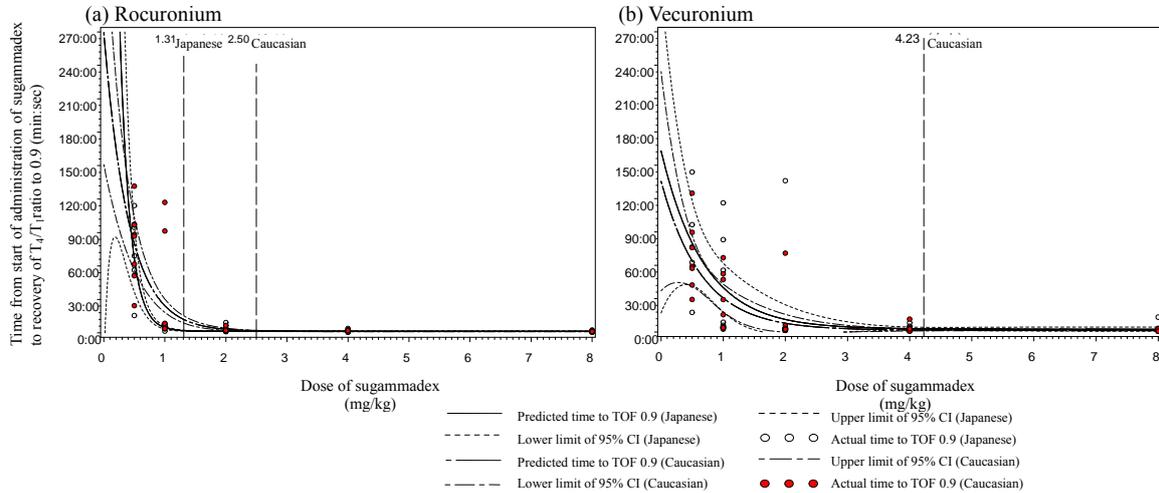
Table B. Difference in the time from administration of 2.0 or 4.0 mg/kg of sugammadex at the reappearance of T₂ after rocuronium or vecuronium administration to recovery of the T₄/T₁ ratio to 0.9 (min:sec) between Japanese and Caucasian subjects (Japanese – Caucasian) (5.3.5.1.8, Trial 19.4.208, PPS)

		Mean ± SD (N)			Trimmed mean difference ^{a)} [95% CI]	Median			Estimated median difference ^{b)} [95% CI]
		2.0 mg/kg group	4.0 mg/kg group	Combined		2.0 mg/kg group	4.0 mg/kg group	Combined	
Rocuronium	Japanese	2:10 ± 1:14 (7)	1:51 ± 1:10 (9)	1:59 ± 1:10 (16)	32.1 [-5.8, 70.1]	1:36	1:38	1:37	13.0 [-5.0, 34.0]
	Caucasian	1:26 ± 0:30 (9)	1:30 ± 0:24 (8)	1:28 ± 0:27 (17)		1:30	1:19	1:25	
Vecuronium	Japanese	2:46 ± 0:50 (6)	2:05 ± 0:54 (10)	2:21 ± 0:55 (16)	-49.2 [-116.7, 18.3]	2:52	1:51	2:18	-25.5 [-71.0, 23.0]
	Caucasian	3:25 ± 1:51 (7)	3:02 ± 2:11 (9)	3:12 ± 2:00 (16)		2:30	2:27	2:29	

- a) A 2-way ANOVA including ethnicity and dose as factors (As the interaction term was not statistically significant [*P* > 0.05], the interaction term was excluded.)
b) As the normality of residuals from the ANOVA model could not be assumed, an additional analysis (nonparametric analysis, Hodges-Lehman estimate) was performed.

For recovery times from administration of different doses of sugammadex at profound neuromuscular blockade (at 1-2 PTCs, 5.3.5.1.9, Trial 19.4.209), the dose-response curves assuming an exponential function (Estimated time to recovery of the T₄/T₁ ratio¹⁴⁾ to 0.9 (dose) = E₀ + b × e^(-c×dose), the coefficients of the dose-response equation, the estimated fastest achievable recovery times, and the estimated smallest doses were as shown in the following figures and table A. Although the 95% CI for the coefficient b included zero for rocuronium in Japanese subjects, as the overall data were well fitted to the estimated dose-response equation (*P* < 0.001, weighted non-linear regression analysis), a dose response has been considered to be demonstrated. These dose-response curves were similar between Japanese and Caucasian subjects. The differences in the time to recovery of the T₄/T₁ ratio to 0.9 between Japanese and Caucasian subjects at doses equal to or higher than the estimated smallest dose were as shown in the following table B, and the 95% CI for the median difference estimated by an additional analysis (Hodges-Lehman estimate) lied within the equivalence interval (ranged from -1 minute

to 1 minute) for both rocuronium and vecuronium. Therefore, the applicant concluded that the similarity between Japanese and Caucasian subjects has been demonstrated.



Figures. Time from administration of 0.5-8 mg/kg of sugammadex at 1-2 PTCs after rocuronium (a) or vecuronium (b) administration to recovery of the T_4/T_1 ratio to 0.9 (min:sec) in Japanese and Caucasian subjects and the estimated dose-response curve (5.3.5.1.9, Trial 19.4.209, PPS)

Table A. Coefficients of the dose-response equation (an exponential function) for the time from administration of 0.5-8 mg/kg of sugammadex at 1-2 PTCs after rocuronium or vecuronium administration to recovery of the T_4/T_1 ratio to 0.9 in Japanese and Caucasian subjects, the estimated fastest achievable recovery times, and the estimated smallest doses (5.3.5.1.9, Trial 19.4.209, PPS)

		Estimated coefficients of the dose-response equation (exponential function) ^{a)} [95% CI]		Fastest achievable recovery time ^{b)} (E_0) (min:sec)	Smallest dose ^{c)} (mg/kg)
		b	c		
Japanese	Rocuronium	1301 [-31.2, 2633]	-5.98 [-7.26, -4.71]	1:28	1.31
	Vecuronium	160.4 [15.6, 305.1]	-1.46 [-2.65, -0.26]	2:41	- ^{d)}
Caucasian	Rocuronium	268.2 [149.8, 386.6]	-2.45 [-2.85, -2.06]	1:14	2.50
	Vecuronium	134.0 [35.5, 232.5]	-1.53 [-2.49, -0.58]	1:42	4.23

a) The estimated coefficients of the dose-response equation (exponential function) “Estimated time to recovery of the T_4/T_1 ratio to 0.9 (dose) = $E_0 + b \times e^{(-c \times \text{dose})}$ ” (weighted non-linear regression analysis)

b) The estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9 (E_0 in the dose-response equation)

c) The dose at which the upper limit of 95% CI of the estimated dose-response curve for the time to recovery of the T_4/T_1 ratio to 0.9 is equal to $E_0 + 1$ minutes

d) The smallest dose could not be calculated due to high variability in the low dose group.

Table B. Difference in the time from administration of 4.0 or 8.0 mg/kg of sugammadex at 1-2 PTCs after rocuronium or vecuronium administration to recovery of the T_4/T_1 ratio to 0.9 between Japanese and Caucasian subjects (Japanese – Caucasian) (5.3.5.1.9, Trial 19.4.209)

		Mean \pm SD (N)			Trimmed mean difference ^{a)} [95% CI]	Median			Estimated median difference ^{b)} [95% CI]
		4.0 mg/kg group	8.0 mg/kg group	Combined		4.0 mg/kg group	8.0 mg/kg group	Combined	
Rocuronium	Japanese	1:35 \pm 0:53 (11)	1:19 \pm 0:34 (10)	1:27 \pm 0:45 (21)	3.3 [-21.1, 27.7]	1:11	1:11	1:11	0 [-14.0, 16.0]
	Caucasian	1:39 \pm 0:39 (10)	1:08 \pm 0:20 (10)	1:24 \pm 0:34 (20)		1:29	1:03	1:13	
Vecuronium	Japanese	3:03 \pm 2:23 (10)	2:56 \pm 3:46 (10)	2:59 \pm 3:04 (20)	33.4 [-77.2, 144.1]	1:56	1:23	1:47	10.5 [-36.0, 59.0]
	Caucasian	3:18 \pm 3:27 (8)	1:39 \pm 0:45 (10)	2:23 \pm 2:26 (18)		2:19	1:38	1:56	

a) A 2-way ANOVA including ethnicity and dose as factors (As the interaction term was not statistically significant ($P > 0.05$), the interaction term was excluded.)

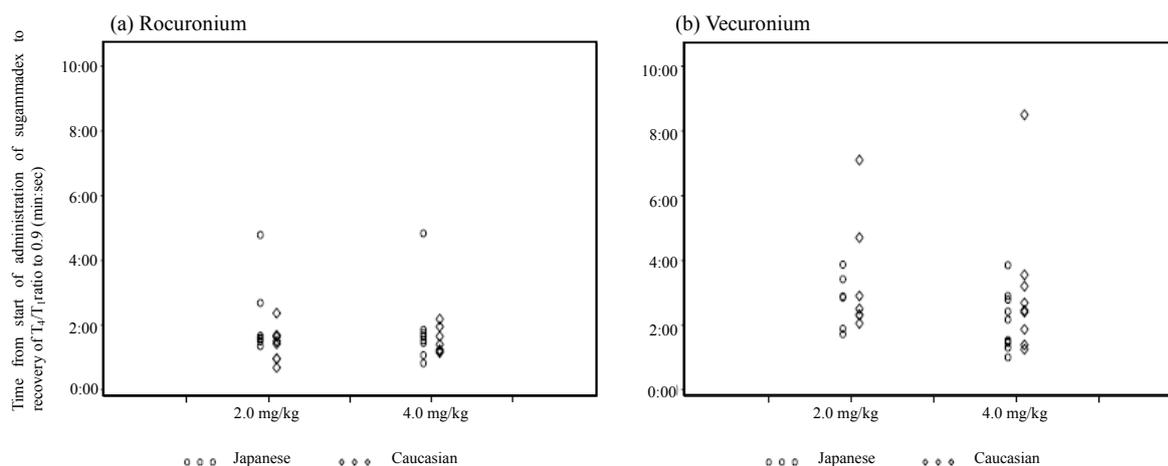
b) As the normality of residuals from the ANOVA model could not be assumed, an additional analysis (nonparametric analysis, Hodges-Lehman estimate) was performed.

PMDA asked the applicant to provide a justification for determining the similarity despite that the CI for the difference between Japanese and Caucasian subjects in the time from administration of sugammadex at the reappearance of T_2 (5.3.5.1.8, Trial 19.4.208) after vecuronium administration to recovery of the T_4/T_1 ratio to 0.9 was not within the pre-defined equivalence interval (ranged from -1 minute to 1 minute).

The applicant explained as follows:

Scatter plots of times from administration of sugammadex at shallow neuromuscular blockade (at the reappearance of T_2) (5.3.5.1.8, Trial 19.4.208) to recovery of the T_4/T_1 ratio to 0.9 are as shown in the following figures. Since the recovery time after vecuronium-induced neuromuscular blockade was prolonged in 1 Caucasian subject in the sugammadex 2.0 mg/kg group and 1 Caucasian subject in 4.0 mg/kg group compared to other Caucasian subjects, an additional analysis (Hodges-Lehman estimate) was performed excluding these 2 subjects.⁶³⁾ As a result, the estimated median difference in the time to recovery of the T_4/T_1 ratio to 0.9 (95% CI) was -9.5 seconds (-52.0 to 30.0 seconds), which lied within the equivalence interval (ranged from -1 minute to 1 minute). Even when these subjects were not excluded, the estimated median difference in the time to recovery of the T_4/T_1 ratio to 0.9 was -25.5 seconds (a negative difference means faster recovery in Japanese subjects compared with Caucasian subjects) and the upper limit of its 95% CI was 23.0 seconds, indicating that the recovery time in Japanese subjects is less than a minute slower compared to that in Caucasian subjects. Therefore, the applicant considered that there is no problem with concluding that the recovery times are clinically comparable between Japanese and Caucasian subjects.

⁶³⁾ Outlier results in 2 Caucasian subjects were both considered attributed to baseline T_4/T_1 ratio of <100% (around 90%) and as recovery from neuromuscular blockade occurred following the discontinuation of sevoflurane used for maintenance anesthesia, the applicant discussed that possible prolongation due to the use of sevoflurane also can not be excluded.



Figures. Time from start of administration of 2 or 4 mg/kg of sugammadex at the reappearance of T_2 after rocuronium (a) or vecuronium (b) to recovery of the T_4/T_1 ratio to 0.9 in Japanese and Caucasian subjects (5.3.5.1.8, Trial 19.4.208, PPS)

4.(ii).B.(2).3 Clinical impact of outliers for the time to recovery of the T_4/T_1 ratio to 0.9

PMDA asked the applicant to explain whether subjects with outliers for the time to recovery of the T_4/T_1 ratio to 0.9 experienced clinically significant residual blockade.

The applicant explained as follows:

For the groups of subjects treated with sugammadex at a dose equal to or higher than the recommended clinical dose (2.0 mg/kg of sugammadex at the reappearance of T_2 , 4.0 mg/kg of sugammadex at 1-2 PTCs) (PPS) in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209), outliers were defined as recovery times >3 times the median recovery time in each group. As a result, 4 subjects⁶⁴⁾ had outliers as shown in the following table, but all of them recovered to a T_4/T_1 ratio of 0.7 or 0.8 as expected and fading of T_2 , T_3 , and T_4 (disappearance of the muscle contraction responses) was not seen. Therefore, the applicant considered that there was no clinically significant residual blockade.

⁶⁴⁾ In the discussion using the distribution of the times to recovery of the T_4/T_1 ratio to 0.9 [see “4.(ii).B.(2).2 Comparison of the time to recovery of the T_4/T_1 ratio to 0.9 between Japanese and Caucasian subjects”], the recovery time in 1 Caucasian subject in the vecuronium-2.0 mg/kg group was visually judged to be an outlier, besides these cases.

Table. Subjects with outliers for the time to recovery of the T₄/T₁ ratio to 0.9 (>3 times the median recovery time in each group) in the groups treated with sugammadex at doses equal to or higher than the recommended clinical dose (PPS) in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209)

Trial Number	Neuromuscular blocking agent	Race	Dose of sugammadex (mg/kg)	Patient demographics			Recovery time (minutes)		
				Age/ Gender	Body weight (kg)	Height (cm)	T ₄ /T ₁ ratio of 0.9	T ₄ /T ₁ ratio of 0.8	T ₄ /T ₁ ratio of 0.7
19.4.208	Vecuronium	Caucasian	4.0	61-year-old female	66	161	8.5	3.5	2.5
19.4.209	Vecuronium	Japanese	4.0	34-year-old female	51	152	8.4	5.4	5.2
			8.0	53-year-old male	60	171	13.5	1.5	1.2
		Caucasian	4.0	48-year-old female ^{a)}	75	172	11.7	11.4	2.9

a) As the depth of neuromuscular blockade was <1-2 PTCs, the applicant discussed that something artificial happened.

4.(ii).B.(2).4) Comparison of safety between Japanese and Caucasian subjects

PMDA asked the applicant to explain the occurrence of adverse events in Japanese and Caucasian subjects in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209).

The applicant explained as follows:

The main adverse events (including laboratory test abnormalities) observed from the day of surgery to the first postoperative day in phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) were as shown in the following tables A and B. Although the incidences of procedural pain and pyrexia were higher in Japanese subjects than Caucasian subjects, as the placebo group also had higher incidences, these events are not considered related to sugammadex. There were no differences in the trend of other adverse events between Japanese and Caucasian subjects and no dose-dependent incidence of any adverse event was seen. Most of adverse events observed from the day of surgery to 7 days after surgery (≥95.0%) occurred from the day of surgery to the first postoperative day. Thus, adverse events observed from the day of surgery to 7 days after surgery showed a similar onset tendency.

Table A. Main adverse events observed from the day of surgery to the first postoperative day in Japanese and Caucasian subjects who received 0.5-4.0 mg/kg of sugammadex at the reappearance of T₂ (Number of subjects with event/Number of subjects included in safety evaluation) (5.3.5.1.8, Trial 19.4.208)

Adverse event	Neuromuscular blocking agent	Japanese					Caucasian				
		Placebo group	Sugammadex groups (mg/kg)				Placebo group	Sugammadex groups (mg/kg)			
			0.5	1.0	2.0	4.0		0.5	1.0	2.0	4.0
Any adverse event	Roc	10/10	9/10	10/10	9/10	8/9	9/10	10/10	6/9	10/10	10/10
	Vec	10/10	9/10	9/10	8/9	9/10	8/10	10/10	6/10	9/10	7/9
	Total (%)	20/20 (100)	18/20 (90.0)	19/20 (95.0)	17/19 (89.5)	17/19 (89.5)	17/20 (85.0)	20/20 (100)	12/19 (63.2)	19/20 (95.0)	17/19 (89.5)
Procedural pain	Roc	8/10	6/10	7/10	6/10	8/9	4/10	5/10	3/9	6/10	6/10
	Vec	9/10	7/10	9/10	5/9	8/10	4/10	2/10	3/10	4/10	3/9
	Total (%)	17/20 (85.0)	13/20 (65.0)	16/20 (80.0)	11/19 (57.9)	16/19 (84.2)	8/20 (40.0)	7/20 (35.0)	6/19 (31.6)	10/20 (50.0)	9/19 (47.4)
Nausea	Roc	2/10	4/10	4/10	4/10	4/9	3/10	4/10	3/9	5/10	4/10
	Vec	4/10	5/10	4/10	5/9	0/10	3/10	4/10	1/10	2/10	4/9
	Total (%)	6/20 (30.0)	9/20 (45.0)	8/20 (40.0)	9/19 (47.4)	4/19 (21.1)	6/20 (30.0)	8/20 (40.0)	4/19 (21.1)	7/20 (35.0)	8/19 (42.1)
Pyrexia	Roc	4/10	3/10	3/10	2/10	3/9	0/10	0/10	0/9	0/10	0/10
	Vec	5/10	4/10	2/10	4/9	2/10	0/10	0/10	0/10	1/10	1/9
	Total (%)	9/20 (45.0)	7/20 (35.0)	5/20 (25.0)	6/19 (31.6)	5/19 (26.3)	0/20 (0)	0/20 (0)	0/19 (0)	1/20 (0.05)	1/19 (0.05)

Roc: rocuronium, Vec: vecuronium

Table B. Main adverse events observed from the day of surgery to the first postoperative day in Japanese and Caucasian subjects who received 0.5-8.0 mg/kg of sugammadex at 1-2 PTCs (Number of subjects with event/Number of subjects included in safety evaluation) (5.3.5.1.9, Trial 19.4.209)

Adverse event	Neuromuscular blocking agent	Japanese					Caucasian				
		Sugammadex groups (mg/kg)					Sugammadex groups (mg/kg)				
		0.5	1.0	2.0	4.0	8.0	0.5	1.0	2.0	4.0	8.0
Any adverse event	Roc	9/9	9/9	10/10	10/11	10/10	6/9	8/10	8/10	9/11	7/10
	Vec	10/10	9/10	10/10	9/10	10/10	5/9	6/10	7/11	6/10	8/11
	Total (%)	19/19 (100)	18/19 (94.7)	20/20 (100)	19/21 (90.5)	20/20 (100)	11/18 (61.1)	14/20 (70.0)	15/21 (71.4)	15/21 (71.4)	15/21 (71.4)
Procedural pain	Roc	8/9	8/9	7/10	9/11	8/10	3/9	4/10	2/10	4/11	3/10
	Vec	7/10	6/10	7/10	6/10	7/10	0/9	3/10	3/11	3/10	3/11
	Total (%)	15/19 (78.9)	14/19 (73.4)	14/20 (70.0)	15/21 (71.4)	15/20 (75.0)	3/18 (16.7)	7/20 (35.0)	5/21 (23.8)	7/21 (33.3)	6/21 (28.6)
Nausea	Roc	1/9	5/9	3/10	2/11	5/10	4/9	4/10	3/10	2/11	3/10
	Vec	2/10	4/10	2/10	4/10	3/10	1/9	3/10	1/11	3/10	3/11
	Total (%)	3/19 (15.8)	9/19 (47.4)	5/20 (25.0)	6/21 (28.6)	8/20 (40.0)	5/18 (27.8)	7/20 (35.0)	4/21 (19.0)	5/21 (23.8)	6/21 (28.6)
Pyrexia	Roc	3/9	2/9	3/10	4/11	3/10	1/9	0/10	0/10	0/11	0/10
	Vec	3/10	2/10	3/10	5/10	1/10	1/9	0/10	0/11	1/10	0/11
	Total (%)	12/19 (63.2)	4/19 (21.1)	6/20 (30.0)	9/21 (42.9)	4/20 (20.0)	2/18 (11.1)	0/20 (0)	0/21 (0)	1/21 (0.05)	0/20 (0)

Roc: rocuronium, Vec: vecuronium

Based on the above, PMDA considers as follows:

The criteria for allowing bridging the clinical data between the two regions, as planned by the applicant in advance, were not fulfilled. However, there were no major differences in the time from start of administration of sugammadex at doses equal to or higher than the recommended clinical dose (≥ 2.0 mg/kg at the reappearance of T₂ or ≥ 4.0 mg/kg at 1-2 PTCs) to recovery of the T₄/T₁ ratio to 0.9 between Japanese and Caucasian subjects, the clinical impact in subjects with prolonged times to recovery of the T₄/T₁ ratio to 0.9 is considered insignificant, and there were no major differences in the occurrence of adverse events. Therefore, there is no major problem with concluding, based on the results from the phase II bridging studies (5.3.5.1.8,

Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209), that the dose-response relationship of sugammadex at doses equal to or higher than the recommended clinical dose is almost similar between Japanese and Caucasian subjects, and evaluating the efficacy and safety of sugammadex, using foreign clinical data.

4.(ii).B.(3) Justification for dosage and administration of sugammadex

4.(ii).B.(3).1) Dosage and administration for the reversal of shallow neuromuscular blockade (at the reappearance of T₂) and profound neuromuscular blockade (at 1-2 PTCs)

PMDA asked the applicant to explain the dosing rationale for sugammadex for routine reversal of shallow neuromuscular blockade (at the reappearance of T₂) and profound neuromuscular blockade (at 1-2 PTCs), taking account of differences in the dose-response relationship between phase II bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) and other trials.

The applicant explained as follows:

The dose-response relationship of sugammadex in reversing shallow neuromuscular blockade (at the reappearance of T₂) and profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after 0.6 mg/kg of rocuronium⁶⁵) was investigated in Japanese and foreign trials.⁶⁶ As a result, the times to recovery of the T₄/T₁ ratio to 0.9 were as shown in the following tables A and B. The recovery times were slightly longer in phase II bridging studies under maintenance anesthesia with sevoflurane (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) compared with other trials under maintenance anesthesia with propofol, which were likely the result of the ability of sevoflurane to enhance neuromuscular blockade (Lowry DW et al. *Anesth Analg.* 1998;87:936-940.). Meanwhile, the influence of the use of sevoflurane vs. propofol maintenance anesthesia was assessed in foreign trials (5.3.5.1.10, Trial 19.4.210; 5.3.5.1.17, Trial 19.4.312), which showed that the reversal of neuromuscular blockade by sugammadex under maintenance anesthesia with sevoflurane was equivalent to that under maintenance anesthesia with propofol. Therefore, the applicant considered that no sugammadex dose adjustment is required regardless of the maintenance anesthetic used.

⁶⁵ The groups of subjects received sugammadex at 15 minutes after rocuronium administration in Foreign Trial 19.4.202 (5.3.5.1.2). As it has been reported that the time to a first response to PTC was about 12 minutes after administration of 0.6 mg/kg of rocuronium (Schultz P et al. *Acta Anaesthesiol Scand.* 2001;45:612-617.), it is generally recognized that the depth of blockade 15 minutes after rocuronium corresponds well with a blockade at 1-2 PTCs.

⁶⁶ The results from the following trials were compared: 5 trials for the reversal of rocuronium-induced neuromuscular blockade at the reappearance of T₂ (5.3.5.1.1, Trial 19.4.201; 5.3.5.1.3, Trial 19.4.203; 5.3.5.1.7, Trial 19.4.207; 5.3.5.1.8, Trial 19.4.208; 5.3.5.1.12, Trial 19.4.306), 2 trials for the reversal of vecuronium-induced neuromuscular blockade at the reappearance of T₂ (5.3.5.1.7, Trial 19.4.207; 5.3.5.1.8, Trial 19.4.208), 2 trials for the reversal of rocuronium-induced neuromuscular blockade at 1-2 PTCs (5.3.5.1.4, Trial 19.4.204; 5.3.5.1.9, Trial 19.4.209), and 1 trial for the reversal of vecuronium-induced neuromuscular blockade at 1-2 PTCs (5.3.5.1.9, Trial 19.4.209). The results from 1 trial of sugammadex administered at 15 minutes after rocuronium administration (5.3.5.1.2, Trial 19.4.202) were compared as the results from trials for the reversal of rocuronium-induced neuromuscular blockade at 1-2 PTCs.

Table A. Time from administration of 0.5-8.0 mg/kg sugammadex at shallow neuromuscular blockade (at the reappearance of T₂) to recovery of the T₄/T₁ ratio to 0.9 (minutes)

Neuromuscular blocking agent	Trial Number	Placebo group	Sugammadex groups (mg/kg)						
			0.5	1.0	2.0	3.0	4.0	6.0	8.0
Rocuronium	19.4.201	23.1 ± 8.8 (4)	5.0 ± 2.8 (5)	3.2 ± 1.7 (4)	1.3 ± 0.4 (3)	1.5 ± 1.0 (5)	1.2 ± 0.2 (3)	-	-
	19.4.203	-	6.8 ± 3.1 (4)	2.7 ± 1.0 (4)	1.8 ± 0.6 (6)	-	1.4 ± 0.6 (6)	2.6 ± 1.3 (4)	-
	19.4.207	31.8 ± 21.0 (2)	3.7 ± 1.0 (8)	2.3 ± 0.9 (7)	1.7 ± 0.6 (8)	1.9 ± 1.2 (3)	1.1 ± 0.3 (8)	-	-
	19.4.208A ^{a)}	82.1 ± 27.6 (6)	3.9 ± 2.5 (5)	2.5 ± 1.3 (10)	2.2 ± 1.2 (7)	-	1.8 ± 1.2 (9)	-	-
	19.4.208B ^{b)}	96.3 ± 33.1 (7)	16.3 ± 20.6 (8)	4.6 ± 6.0 (8)	1.4 ± 0.5 (9)	-	1.5 ± 0.4 (8)	-	-
	19.4.306 ^{b)}	29.5 ± 8.4 (6)	3.8 ± 1.1 (5)	1.6 ± 0.3 (5)	1.3 ± 0.3 (5)	-	1.4 ± 0.4 (5)	-	-
	Pooled trials	60.0 ± 38.8 (25)	7.2 ± 10.8 (35)	2.9 ± 2.9 (38)	1.6 ± 0.7 (38)	1.6 ± 1.0 (8)	1.4 ± 0.7 (39)	2.6 ± 1.3 (4)	-
Vecuronium	19.4.207	48.7 ± 27.9 (4)	7.7 ± 2.6 (6)	2.5 ± 0.8 (8)	2.3 ± 0.8 (8)	-	1.5 ± 0.5 (7)	-	1.4 ± 0.5 (4)
	19.4.208A	83.2 ± 20.6 (7)	52.0 ± 64.9 (3)	10.6 ± 19.2 (8)	2.8 ± 0.8 (6)	-	2.1 ± 0.9 (10)	-	-
	19.4.208B	79.0 ± 26.0 (8)	35.5 ± 42.1 (9)	5.1 ± 2.4 (10)	3.4 ± 1.9 (7)	-	3.0 ± 2.2 (9)	-	-
	Pooled trials	74.2 ± 26.8 (19)	29.0 ± 40.1 (18)	6.0 ± 10.8 (26)	2.8 ± 1.3 (21)	-	2.3 ± 1.5 (26)	-	1.4 ± 0.5 (4)

Mean ± SD (Number of subjects evaluated), -: Not applicable, See the footnote of the text for the document number of each trial.

a) As Trial 19.4.208, Trial 19.4.208A in Japanese subjects and Trial 19.4.208B in Caucasian subjects were conducted using the identical protocol.

b) Adult data only

Table B. Time from administration of 0.5-8.0 mg/kg sugammadex at profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after 0.6 mg/kg of rocuronium) to recovery of the T₄/T₁ ratio to 0.9 (minutes)

Neuromuscular blocking agent	Trial Number	Placebo group	Sugammadex groups (mg/kg)					
			0.5	1.0	2.0	4.0	6.0	8.0
Rocuronium	19.4.202 ^{a)}	35.6 ± 9.0 (3)	-	6.5 ± 1.7 (6)	2.7 ± 0.7 (6)	2.0 ± 1.2 (6)	2.1 ± 2.0 (6)	1.3 ± 0.2 (6)
	19.4.204	-	38.3 ± 30.6 (4)	14.5 ± 13.6 (5)	5.0 ± 4.3 (8)	2.6 ± 1.3 (4)	-	1.3 ± 0.5 (8)
	19.4.209A ^{b)}	-	66.9 ± 34.6 (6)	4.7 ± 1.7 (7)	3.4 ± 2.5 (10)	1.6 ± 0.9 (11)	-	1.3 ± 0.6 (10)
	19.4.209B ^{b)}	-	79.8 ± 33.0 (8)	28.0 ± 43.7 (9)	3.2 ± 1.5 (10)	1.6 ± 0.7 (10)	-	1.1 ± 0.3 (10)
	Pooled trials	35.6 ± 9.0 (3)	66.3 ± 35.2 (18)	14.7 ± 26.9 (27)	3.6 ± 2.6 (34)	1.8 ± 1.0 (31)	2.1 ± 2.0 (6)	1.3 ± 0.4 (34)
Vecuronium	19.4.209A ^{b)}	-	79.5 ± 46.2 (5)	39.8 ± 45.8 (7)	16.0 ± 42.2 (10)	3.0 ± 2.4 (10)	-	2.9 ± 3.8 (10)
	19.4.209B ^{b)}	-	68.4 ± 31.9 (7)	25.1 ± 24.9 (9)	9.1 ± 20.6 (11)	3.3 ± 3.5 (8)	-	1.7 ± 0.7 (10)
	Pooled trials	-	73.0 ± 37.0 (12)	31.6 ± 35.0 (16)	12.4 ± 32.0 (21)	3.2 ± 2.8 (18)	-	2.3 ± 2.7 (20)

Mean ± SD (Number of subjects evaluated), -: Not applicable, See the footnote of the text for the document number of each trial.

a) Recovery times with sugammadex administered at 15 minutes after 0.6 mg/kg of rocuronium in Trial 19.4.202

b) As Trial 19.4.209, Trial 19.4.209A in Japanese subjects and Trial 19.4.209B in Caucasian subjects were conducted using the identical protocol.

Then, the applicant explained as follows:

The recommended clinical doses of sugammadex should “minimize the possibility of incomplete recovery (residual neuromuscular blockade),” “provide reductions in recovery time compared to spontaneous recovery and currently available reversal agents,” and “provide limited choice of doses in order to minimize the risk of confusion regarding use.” According to the results presented in the above tables A and B, a dose-response relationship was observed for the time to recovery of the T_4/T_1 ratio to 0.9 for both shallow neuromuscular blockade (at the reappearance of T_2) and profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after 0.6 mg/kg of rocuronium). The mean time to recovery from shallow neuromuscular blockade (at the reappearance of T_2) in the sugammadex 2.0 mg/kg group and the mean time to recovery from profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after rocuronium administration) in the sugammadex 4.0 mg/kg group were 2.8 and 3.2 minutes, respectively, for vecuronium-induced neuromuscular blockade, and the recovery times were longer compared with the mean times to recovery from rocuronium-induced neuromuscular blockade (1.6 and 1.8 minutes, respectively). However, these recovery times observed are considered clinically significant compared with those in the placebo groups (60-74.2 and 35.6 minutes, respectively). Doubling the dose of sugammadex (4.0 and 8.0 mg/kg, respectively) resulted in only a slight reduction in the mean recovery time (0.2-0.9 minutes).

Furthermore, the applicant explained as follows:

Tolerance intervals containing different proportions of subjects who will recover to a T_4/T_1 ratio of ≥ 0.9 for 2 mg/kg of sugammadex administered at shallow neuromuscular blockade (at the reappearance of T_2) or 4 mg/kg of sugammadex administered at profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after rocuronium administration) are as shown in the following table C. It can be expected with 97.5% confidence that a majority (90%) of patients will recover within 3.0 or 5.9 minutes following administration of sugammadex at shallow neuromuscular blockade (at the reappearance of T_2) after rocuronium or vecuronium administration, respectively, and within 3.9 or 11.0 minutes following administration of sugammadex at profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after 0.6 mg/kg of rocuronium administration) after rocuronium or vecuronium administration, respectively.

Table C. Upper limits of tolerance intervals containing different proportions of subjects who will recover to a T_4/T_1 ratio of ≥ 0.9 for 2.0 mg/kg sugammadex administered at shallow neuromuscular blockade (at the reappearance of T_2) or 4.0 mg/kg sugammadex administered at profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after 0.6 mg/kg rocuronium) (minutes) (97.5% confidence) (PPS)

Proportion of subjects who will recover to a T_4/T_1 ratio of ≥ 0.9 within the upper limit	Shallow neuromuscular blockade (at the reappearance of T_2) ^{a)}		Profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after rocuronium administration) ^{b)}	
	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg	
	Rocuronium	Vecuronium	Rocuronium	Vecuronium
80%	2.5	4.7	3.0	7.2
85%	2.7	5.2	3.4	8.7
90%	3.0	5.9	3.9	11.0
95%	3.6	7.2	4.8	15.8

a) Pooled results from Trial 19.4.201, Trial 19.4.203, Trial 19.4.207, Trial 19.4.208A, Trial 19.4.208B, and Trial 19.4.306

b) Pooled results from Trial 19.4.202, Trial 19.4.204, Trial 19.4.209A, and Trial 19.4.209B

(See the footnote of the text for the document number of each trial.)

Based on the above, the applicant considered that in order to avoid confusion in medical practice, one dose level should be selected for similar levels of neuromuscular blockade, regardless of the neuromuscular blocking agent used, and concluded that the recommended clinical doses of sugammadex should be 2 mg/kg for the reversal of shallow neuromuscular blockade (at the reappearance of T_2) and 4 mg/kg for the reversal of profound neuromuscular blockade (at 1-2 PTCs or at 15 minutes after 0.6 mg/kg of rocuronium).

4.(ii).B.(3).2) Dosage and administration and re-administration of sugammadex in situations where a neuromuscular monitor can not be used

PMDA asked the applicant to explain dosage and administration of sugammadex for routine reversal in situations where a neuromuscular monitor can not be used.

The applicant explained as follows:

In situations where a neuromuscular monitor can not be used, the recovery of neuromuscular blockade can be assessed by return of spontaneous respiration, and spontaneous respiration generally returns at more shallow blockade than the level of blockade at the reappearance of T_2 (Ali HH et al. *Anesthesiology*. 1976;45:216-249.). Therefore, after the return of spontaneous respiration following rocuronium or vecuronium administration, a dose of 2.0 mg/kg sugammadex should be administered. On the other hand, regarding profound neuromuscular blockade, although there is no definitive clinical indicator of the depth of neuromuscular blockade that corresponds with a blockade at 1-2 PTCs, it has been reported that the time to a first response to PTC was 12 minutes following administration of 0.6 mg/kg of rocuronium (Schultz P et al. *Acta Anaesthesiol Scand*. 2001;45:612-617.). A foreign phase III trial in patients receiving a wide range of surgical procedures and anesthetic regimens (5.3.5.2.1, Trial 19.4.311) confirmed the efficacy and safety of 4.0 mg/kg sugammadex when administered at least 15 minutes after the intubating dose of 0.6 mg/kg rocuronium or the last maintenance dose of 0.15 mg/kg rocuronium. In the trial, the time to recovery of the T_4/T_1 ratio to 0.9 (mean \pm

SD) (Number of subjects evaluated) was 2 minutes: 19 seconds \pm 2 minutes: 09 seconds (N = 177) and 89.3% of the subjects (158 of 177 subjects) recovered to a T_4/T_1 ratio of 0.9 within 4 minutes after sugammadex administration. However, regarding profound neuromuscular blockade after vecuronium administration, although it has been reported that the first response to PTC was seen at 18.4 to 19.8 minutes after administration of 0.1 mg/kg vecuronium (Muchhal KK et al. *Anesthesiology*. 1987;66:846-849.), a clinical trial to evaluate the efficacy and safety of sugammadex when administered at this timepoint has not been conducted and the recommended dosage and administration has not been established for the reversal of profound vecuronium-induced neuromuscular blockade in situations where a neuromuscular monitor can not be used. Thus, it should be stated in the “Precautions for Dosage and Administration” section of the package insert that a dose of 2 mg/kg should be administered after the return of spontaneous respiration and a dose of 4 mg/kg should be administered at least 15 minutes after the intubating dose of 0.6 mg/kg rocuronium or the last maintenance dose of rocuronium. The use of a neuromuscular monitor as appropriate should be advised in the “Important Precautions” section of the package insert.

PMDA asked the applicant to explain dosage and administration when sugammadex is used for the reversal of moderate neuromuscular blockade (i.e., a level of neuromuscular blockade between the level of blockade at the reappearance of T_2 and the level of blockade at 1-2 PTCs).

The applicant explained that in order to reduce the risk of residual blockade due to sub-optimal doses of sugammadex, a dose of 4 mg/kg of sugammadex is recommended for the reversal of moderate neuromuscular blockade in situations where a neuromuscular monitor can be used.

4.(ii).B.(3).3) Use of sugammadex for immediate reversal

A clinical trial in an immediate reversal setting assuming a CICV (Cannot Intubate - Cannot Ventilate) situation [see “4.(ii).B.(1) Clinical positioning of sugammadex”] has not been conducted in Japanese patients and the maximum approved dose of rocuronium is different between Japan and overseas (0.9 mg/kg in Japan, 1.0 mg/kg in the EU, 1.2 mg/kg in the US). Thus, PMDA asked the applicant to explain the basis for the recommended dose of 16 mg/kg of sugammadex in Japanese patients for immediate reversal.

The applicant explained as follows:

When 2.0 to 16.0 mg/kg of sugammadex was administered at 3 minutes after 1.0 or 1.2 mg/kg of rocuronium (5.3.5.1.6, Trial 19.4.206) or at 5 minutes after 1.2 mg/kg of rocuronium (5.3.5.1.5, Trial 19.4.205) assuming a CICV situation, the recovery times to a T_4/T_1 ratio of 0.9

were as shown in the following table A. The differences between the doses of 12.0 and 16.0 mg/kg of sugammadex were small. However, taking account of tolerance intervals that contain different proportions of subjects who will recover to a T_4/T_1 ratio of ≥ 0.9 for 16 mg/kg sugammadex administered at 3 or 5 minutes after rocuronium administration as shown in the following table B, a recommended clinical dose of 16 mg/kg of sugammadex for immediate reversal has been chosen as a dose well in excess of what is required to achieve reversal of neuromuscular blockade.

Table A. Time from administration of 2.0-16.0 mg/kg sugammadex at 3 or 5 minutes after 1.0 or 1.2 mg/kg rocuronium to recovery of the T_4/T_1 ratio to 0.9 (minutes)

Dose of rocuronium and time after rocuronium administration		Trial Number	Placebo group	Sugammadex groups (mg/kg)				
				2.0	4.0	8.0	12.0	16.0
1.0 mg/kg	3 minutes	19.4.206	108:26 ± 31:10 (5)	44:44 ± 22:11 (11)	6:56 ± 2:52 (11)	2:24 ± 1:10 (11)	2:25 ± 2:07 (11)	1:46 ± 1:08 (10)
			122:59 ± 28:28 (4)	65:40 ± 24:35 (9)	13:47 ± 7:38 (8)	3:14 ± 0:59 (11)	2:05 ± 0:51 (10)	1:19 ± 0:25 (11)
1.2 mg/kg	5 minutes	19.4.205	122:05 ± 18:05 (4)	56:30 ± 5:22 (5)	15:47 ± 17:45 (5)	2:45 ± 0:33 (12)	1:23 ± 0:19 (7)	1:55 ± 2:13 (7)

Mean ± SD (Number of subjects evaluated)

Table B. Tolerance intervals for sugammadex (16.0 mg/kg) administered for immediate reversal (3 or 5 minutes after 1.0 or 1.2 mg/kg rocuronium) (97.5% confidence) (PPS)

Proportion of subjects who will recover to $T_4/T_1 \geq 0.9$ within the upper limit	Upper limit of tolerance interval (minutes)	
	An outlier ^{a)} is included	An outlier ^{a)} is excluded
80%	2.9	1.9
85%	3.3	2.1
90%	3.9	2.3
95%	5.1	2.7

Pooled results from Trial 19.4.205 and Trial 19.4.206

a) One subject had a relatively prolonged recovery time (6.9 minutes), likely due to technical issues with neuromuscular monitoring. Upper limits of tolerance intervals were calculated both including and excluding this subject.

The maximum intubating dose of rocuronium in Japan is 0.9 mg/kg, which may lead to a lower plasma rocuronium concentration early after its administration compared with 1.0 or 1.2 mg/kg. However, in an immediate reversal setting, it is necessary to select a dose of sugammadex well in excess of what is required to achieve reversal of rocuronium-induced neuromuscular blockade. Under such situations, a slight difference in the plasma rocuronium concentration should have no clinical impact. Meanwhile, the dose response relationship of sugammadex administered at doses of 0.5 to 4.0 mg/kg at the reappearance of T_2 or at doses of 0.5 to 8.0 mg/kg at 1-2 PTCs was similar between Japanese and Caucasian subjects [see “4.(ii).B.(2).2) Comparison of the time to recovery of the T_4/T_1 ratio to 0.9 between Japanese and Caucasian subjects”]. Therefore, it is inferred that there are also no major differences between Japanese and Caucasian subjects in the recovery time with 16.0 mg/kg sugammadex administered for immediate reversal and the efficacy of 16.0 mg/kg of sugammadex can be expected also for immediate reversal following an intubating dose of 0.9 mg/kg rocuronium in Japanese patients. Furthermore, in a phase I trial in Japanese and Caucasian healthy adult subjects (5.3.3.3.1, Trial 19.4.102), no major differences between Japanese and Caucasian subjects in the

pharmacokinetics of 16.0 mg/kg of sugammadex were observed [see “4.(i) Summary of human pharmacokinetic and pharmacodynamic trials”] and there were also no particular safety problems. A foreign phase I trial (5.3.3.1.4, Trial 19.4.106) confirmed the tolerability of sugammadex at doses up to 96 mg/kg. Therefore, a 16 mg/kg dose of sugammadex is considered possible to be used safely also in Japanese patients. Although CICV is a life-threatening, unsafe situation, as its incidence is low, it is difficult to conduct a clinical trial in patients in CICV situations. A foreign phase III trial assuming a CICV situation (5.3.5.1.16, Trial 19.4.303) was conducted in patients who did not require a neuromuscular blocking agent after endotracheal intubation. In foreign countries, a non-steroidal neuromuscular blocking agent, atracurium (unapproved in Japan) etc. can be used if neuromuscular blockade is required during surgery after sugammadex administration. On the other hand, in Japan, as a non-steroidal, non-depolarizing neuromuscular blocking agent is unapproved, it is difficult to conduct a similar trial.

Based on the above, PMDA considers as follows:

There is no major problem with recommending a dose of 2 mg/kg and 4 mg/kg for routine reversal at the reappearance of T₂ and at 1-2 PTCs, respectively, as detected with a neuromuscular monitor. Precautions of dosage and administration of sugammadex in situations where a neuromuscular monitor can not be used, will be determined, taking account of comments from the Expert Discussion.

Regarding a 16 mg/kg dose of sugammadex recommended for immediate reversal, although there are no clinical trial data from Japanese patients, foreign trial data have suggested that sugammadex will be an effective reversal agent even in a life-threatening CICV situation and similar efficacy can be expected also in Japanese patients. Also as to safety, the tolerability of 16 mg/kg of sugammadex in Japanese healthy adult subjects and the tolerability of sugammadex at doses up to 96 mg/kg in foreign subjects have been confirmed. Therefore, there is no serious concern about recommending the same dosage regimen as in the EU for Japanese patients, provided that information on Japanese patients will be collected as much as possible and analyzed after the market launch. However, for patients in whom intubation difficulties are anticipated, a method of securing an airway should be selected, fully balancing the risks and benefits of sugammadex vs. alternatives without using a neuromuscular blocking agent (e.g. intubation while maintaining spontaneous respiration) and it should be noted that rocuronium in combination with sugammadex should not be used without due consideration for rapid sequence induction etc. These opinions of PMDA will be discussed at the Expert Discussion.

4.(ii).B.(4) Safety of sugammadex

4.(ii).B.(4).1) Re-occurrence of blockade or residual blockade after sugammadex administration

PMDA asked the applicant to explain the risk of re-occurrence of blockade and residual blockade after sugammadex administration.

The applicant explained as follows:

Adverse events representative of re-occurrence of blockade or residual blockade⁶⁷⁾ occurred in 0.4% (7 of 1738 subjects) of the sugammadex group in pooled Japanese and foreign phase II and III trials³⁰⁾ and 2.4% (4 of 167 subjects) of the neostigmine group in pooled foreign phase II and III trials with a neostigmine group (5.3.5.1.13, Trial 19.4.301; 5.3.5.1.15, Trial 19.4.302). Of these, 2 subjects received sugammadex at doses equal to or greater than the recommended clinical doses, i.e. 16.0 mg/kg for immediate reversal (both subjects had recurarization). In pooled Japanese and foreign phase II and III trials,³⁰⁾ 1.4% (24 of 1738 subjects) of the sugammadex group had a decline in the T_4/T_1 ratio to ≤ 0.8 after recovery to 0.9 in at least three consecutive TOF values, as measured using a neuromuscular monitor. Of these, 3 subjects received sugammadex at doses equal to or greater than the recommended clinical doses, i.e. 2 subjects received 2.0 mg/kg at the reappearance of T_2 and 1 subject received 16.0 mg/kg for immediate reversal (the same subject as the one who experienced an adverse event of recurarization). Given that it has been reported that 13% to 88% of patients who received conventional reversal agents such as neostigmine experienced re-occurrence of blockade (Fezing AK et al. *Acta Anaesthesiol Belg.* 1999;50:83-86, Baillard C et al. *Br J Anesth.* 2000;84:394-395, Cammu G et al. *Anesth Analg.* 2006;102:426-429, Hayes AH et al. *Anesthesia.* 2001;56:312-618, Murphy GS et al. *Anesth Analg.* 2005;100:1840-1845.), the risk of re-occurrence of blockade or residual blockade after sugammadex administration is considered very low compared to conventional reversal agents. However, since the possibility of re-occurrence of blockade after administration of magnesium or aminoglycoside antibiotics etc. following sugammadex administration can not be ruled out [see “3.(i).B.(2) Pharmacodynamic interactions and the influences on neuromuscular blockade”], in case re-occurrence of blockade is observed after an initial dose of 2 mg/kg or 4 mg/kg sugammadex, a repeat dose of 4 mg/kg sugammadex should be administered.

⁶⁷⁾ Adverse events were identified by the MedDRA Preferred Terms: neuromuscular block prolonged, neuromuscular blockade, and recurarization.

PMDA considers as follows:

Although re-occurrence of blockade or residual blockade after sugammadex administration is unlikely to become a clinically relevant problem at present, a further investigation is needed via post-marketing surveillance etc. As a clinical trial on sugammadex re-administration has not been conducted either in Japan or overseas, at present, there is no scientific evidence for recommending a repeat dose of 4 mg/kg sugammadex in case re-occurrence of blockade is observed.

4.(ii).B.(4).2) Hypersensitivity and allergic reactions

As one subject had an allergic reaction to sugammadex in a high-dose safety trial in foreign healthy adult subjects (5.3.3.1.4, Trial 19.4.106), PMDA asked the applicant to explain the risk of hypersensitivity and allergic reactions to sugammadex.

The applicant explained as follows:

As shown in the following table, clinical findings suggestive of hypersensitivity or allergic reactions were reported by a total of 12 subjects in pooled Japanese and foreign clinical trials (i.e., 8 subjects in foreign phase I trials and 4 subjects in foreign phase III trials, but not by Japanese subjects).

Table. Subjects with clinical findings suggestive of hypersensitivity in pooled Japanese and foreign phase I-III trials (all foreign subjects)

Trial Number	Age/Gender	History of allergy	Sugammadex (at the onset of hypersensitivity)		Clinical findings	Skin tests ^{a)}	
			Dose (mg/kg)	No. of exposures (time interval between exposures)			
Phase I trials	19.4.106	27-year-old male	None	8.4 ^{c)}	1	paraesthesia, tachycardia, nausea, palpitations, stomach discomfort, dysgeusia, visual disturbance, flushing, rash erythematous	Positive ^{b)}
	19.4.105	42-year-old female	None	4.0, 32	2 (14 days)	Following a dose of 4.0 mg/kg (first exposure): diarrhoea, pustule and itching (chest, back, face) Following a dose of 32 mg/kg (second exposure): abnormal sensation of limbs, hot feeling in hands and feet, dizziness, throat tightness, dyspnoea, tachycardia, flushing	Negative ^{b)}
		33-year-old female	Penicillin allergy	32	2	Rash with itch (neck, the upper part of the body)	Negative ^{b)}
		36-year-old female	None	32	1	palpitations, heart rate increased, tachycardia, ventricular extrasystoles, flushing (chest), respiratory rate increased	Negative ^{b)}
		35-year-old female	Lactose intolerance	32	2 (6 days)	urge of sneezing, globus feeling, nasal congestion	Negative ^{b)}
		41-year-old female	None	32	1 ^{d)}	rash (the upper part of the body)	Unknown
	19.4.109	39-year-old female	None	32	2 (8 days)	systemic burning sensation, nausea, generalized sensation of heaviness, allergic reaction with agitation, administration site redness, ECG electrode application site rash	Negative ^{b)}
	19.4.115	39-year-old male	Pollinosis	16.0	1	dysgeusia, salivary hypersecretion, urticaria, peripheral coldness, paraesthesia, headache, pollakiuria	Negative

Trial Number	Age/Gender	History of allergy	Sugammadex (at the onset of hypersensitivity)		Clinical findings	Skin tests ^{a)}	
Phase III trials	19.4.302	33-year-old female	Bee allergy	4.0	1	nausea, vomiting, itching, hypotension	Unknown
		65-year-old female		4.0	1	nausea, rash	Unknown
	19.4.308	28-year-old female	Asthma, egg allergy etc.	2.0	1	abdominal pain, itching, nausea, incision site haematoma	Unknown
	19.4.311	32-year-old female	None	4.0	1	nausea, vomiting, hypotension	Unknown

Trial 19.4.106: High-dose safety trial (5.3.3.1.4), Trial 19.4.105 and Trial 19.4.109: QT trials (5.3.3.1.3 and 5.3.3.1.8),

Trial 19.4.115: Study to investigate the effects on hemostasis parameters (Reference data 5.3.3.1.11)

a) Skin prick and intradermal tests, b) Subjects enrolled in Trial 19.4.110 (Reference data 5.3.3.1.9)

c) Although the subject was scheduled to intravenously receive 32 mg/kg sugammadex over 5 minutes, infusion was stopped after 8.4 mg/kg due to adverse events (paraesthesia and visual disturbance).

d) Hypersensitivity or allergic reactions did not occur after the second exposure (other subjects did not receive sugammadex after the development of hypersensitivity or allergic reactions)

In 6 Japanese and foreign phase I trials (5.3.3.1.2, Trial 19.4.101; 5.3.3.3.1, Trial 19.4.102; 5.3.3.1.3, Trial 19.4.105; 5.3.3.1.4, Trial 19.4.106; 5.3.3.1.8, Trial 19.4.109; 5.3.3.1.11, Trial 19.4.115), a total of 201 foreign healthy adult subjects received two to four different doses of sugammadex separated by 7 to 19 days on average in ascending order (≥ 600 doses in total) and among 8 subjects with clinical findings suggestive of hypersensitivity in foreign phase I trials, 5

subjects showed these findings following their first exposure to sugammadex. Six of the 8 subjects had these findings following the administration of 32 mg/kg, which is higher than the recommended clinical doses. No serious or severe adverse events were reported by these subjects.

The potential for sugammadex to induce hypersensitivity or allergic reactions was investigated in the following *ex vivo* or *in vitro* studies. As a result, although it can not be ruled out that sugammadex at doses higher than the recommended clinical doses directly stimulates mast cells through a non-immune mediated mechanism, the definitive mechanism of sugammadex to induce hypersensitivity and allergic reactions has not been identified at present.

- (a) Serum samples from 7 of the 8 subjects with clinical findings suggestive of hypersensitivity or allergic reactions (excluding 1 subject in Trial 19.4.115 [Reference data 5.3.3.1.11]) were tested for antibody to sugammadex by immunoassay. As a result, all samples were negative for antibody to sugammadex (Reference data 5.3.2.3.6).
- (b) A skin prick test was performed in 11 foreign healthy adult subjects not previously exposed to sugammadex, 6 foreign healthy adult subjects previously exposed to sugammadex with clinical findings suggestive of hypersensitivity or allergic reactions reported, and 6 foreign healthy adult subjects previously exposed to sugammadex without clinical findings suggestive of hypersensitivity or allergic reactions reported. As a result, all of them had negative results. An intradermal test was performed in 9 foreign healthy adult subjects not previously exposed to sugammadex, 5 foreign healthy adult subjects previously exposed to sugammadex with clinical findings suggestive of hypersensitivity reported, and 6 foreign healthy adult subjects previously exposed to sugammadex without clinical findings suggestive of hypersensitivity reported. As a result, 2 subjects previously exposed to sugammadex (1 subject with clinical findings suggestive of hypersensitivity or allergic reactions reported and 1 subject without clinical findings suggestive of hypersensitivity or allergic reactions reported) gave a positive response. However, the applicant discussed that the 1 subject without hypersensitivity or allergic reactions reported had an increased level of urine methylhistamine at baseline, which may indicate a false-positive outcome (Reference data 5.3.3.1.9, Trial 19.4.110).
- (c) Using skin specimens obtained during surgery, the effects on mast cells were investigated by microdialysis. In one of the 9 specimens, histamine release was observed at a sugammadex concentration (50 mg/mL), 250-fold higher than the human maximum plasma concentration of unchanged sugammadex at 16.0 mg/kg (0.2 mg/mL). When human basophils isolated from blood obtained from healthy adults were activated by interleukin-3

and directly added with 0.001 to 10 mg/mL of sugammadex, or treated to remove IgE, sensitized with serum from subjects with clinical findings suggestive of hypersensitivity, and then added with 0.001 to 10 mg/mL of sugammadex, histamine release was not observed (Reference data 5.3.2.3.7).

As the safety of sugammadex at >16.0 mg/kg in healthy adult subjects or >8.0 mg/kg in patients has not been studied among the Japanese population, PMDA asked the applicant to explain the possibility of an increased risk of hypersensitivity and allergic reactions at high doses of sugammadex (especially at a dose of 16 mg/kg of sugammadex for immediate reversal) in Japanese patients.

The applicant explained as follows:

In a phase I trial in Japanese and Caucasian healthy adult subjects (5.3.3.3.1, Trial 19.4.102), no hypersensitivity-related adverse events⁶⁸ were reported by Caucasian subjects while 14.3% of Japanese subjects treated with sugammadex (2 of 14 subjects [1 subject each in the 8.0 and 16.0 mg/kg groups]) and 14.3% of Japanese subjects treated with placebo (2 of 14 subjects) had cough or sneezing, which were all mild in severity. In bridging studies (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209), 15.8% (28 of 177 subjects) of Japanese subjects and 5.6% (10 of 179 subjects) of Caucasian subjects experienced cough, dyspnoea, blood pressure decreased, oedema, pruritus, etc., but there were no severe events and moderate events were reported by 2 Japanese subjects (1.1%) and 3 Caucasian subjects (1.7%), showing no major differences. In pooled Japanese and foreign phase II and III trials,³⁰ 11.1% of the sugammadex group ([193 of 1738 subjects] mild, 7.0%; moderate, 3.7%; severe, 0.4%) had pruritus, dyspnoea, cough, hypotension, etc., which were not different in trend from the placebo group (11.5% [15 of 130 subjects] mild, 6.9%; moderate, 3.8%) and there was no dose-dependent increase in the incidence over the dose range of 2.0 to 16.0 mg/kg of sugammadex. Therefore, the possibility of an increased risk particularly in Japanese patients should be low. Since sugammadex is used in the operating room under the supervision of a doctor, even if hypersensitivity or allergic reactions occur, appropriate action can be taken and in a CICV situation requiring immediate reversal, the benefit of the reversal of neuromuscular blockade by sugammadex should outweigh the risk of hypersensitivity.

Based on the above, PMDA considers as follows:

Given that most of the subjects with suspected hypersensitivity or allergic reactions received sugammadex at a dose higher than the maximum recommended clinical dose (16 mg/kg) and

⁶⁸) Adverse events were identified by the MedDRA broad SMQ “Anaphylactic reaction.”

sugammadex is used only under the supervision of a doctor, as long as sugammadex is used properly, complying with the labeled dosage and administration instructions, hypersensitivity and allergic reactions are unlikely to become a clinically relevant problem. It is necessary to continue to investigate the risk of hypersensitivity and allergic reactions to sugammadex after the market launch.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209). As a result, protocol deviations (study drug administration errors) were found at some clinical trial sites. In addition, protocol deviations due to flaws in the protocol (the dose and timing of administration) were noted during an inspection of the sponsor, but PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

IV. Overall Evaluation

Based on the submitted data, PMDA considers that the efficacy and safety of sugammadex in the reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide have been demonstrated. However, dosage and administration of sugammadex for immediate reversal in Japanese patients, dosage and administration of sugammadex in situations where a neuromuscular monitor can not be used, and a precaution statement regarding re-administration of neuromuscular blocking agents after sugammadex administration etc. will be determined, taking account of comments from the Expert Discussion. The safety of sugammadex in an immediate reversal setting, adverse events of bleeding and allergic reactions, re-occurrence of

blockade or residual blockade, the safety of sugammadex in patients with impaired renal or hepatic function and geriatric patients, interactions with drugs affecting neuromuscular blockade, etc. need to be fully investigated via post-marketing surveillance.

PMDA considers that sugammadex may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

October 1, 2009

The Pharmaceuticals and Medical Devices Agency (PMDA)'s conclusions were supported at the Expert Discussion. Taking account of comments from the Expert Discussion, PMDA conducted an additional review of the following points and took necessary actions. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

(1) Dosage and administration of sugammadex and use of a neuromuscular monitor

At the Expert Discussion, there was an opinion that a neuromuscular monitor should be used wherever possible for objective assessment of the degree of neuromuscular blockade and recovery of neuromuscular blockade and the safe and appropriate use of sugammadex. Japanese clinical trials (5.3.5.1.8, Trial 19.4.208; 5.3.5.1.9, Trial 19.4.209) were both conducted using a neuromuscular monitor. Therefore, PMDA concluded that like in the EU, the dosage and administration statement should be based on the assumption that a neuromuscular monitor can be used.

The applicant explained that "a dose of 4 mg/kg sugammadex should be administered at least 15 minutes after the intubating dose of 0.6 mg/kg rocuronium or the last maintenance dose of rocuronium" for the reversal of profound neuromuscular blockade before the return of adequate spontaneous respiration in situations where a neuromuscular monitor can not be used [see Review Report (1) "4.(ii).B.(3).2) Dosage and administration and re-administration of sugammadex in situations where a neuromuscular monitor can not be used"]. However, since the maximum approved dose of rocuronium in Japan is 0.9 mg/kg and about two-thirds of rocuronium-treated patients received an intubating dose of >0.6 mg/kg in routine clinical practice (the 4th periodic safety update report for Esclax; the period covered, from October 2, 2007 to March 16, 2009; 99 cases surveyed), PMDA instructed the applicant; (a) to reconsider the above dosing instruction taking account of this finding; and (b) include a precaution statement in the package insert that the efficacy and safety of sugammadex in the reversal of profound vecuronium-induced neuromuscular blockade in situations where a neuromuscular monitor can not be used have not been established.

The applicant explained as follows:

In a foreign phase II trial (5.3.5.1.6, Trial 19.4.206), the time from administration of 4 mg/kg sugammadex at 3 or 15 minutes after 1.0 mg/kg rocuronium to recovery of the T_4/T_1 ratio¹⁴⁾ to 0.9 (mean \pm SD) was 6 minutes: 56 seconds \pm 5 minutes: 52 seconds or 5 minutes: 28 seconds \pm 3 minutes: 08 seconds, respectively, which was sufficiently faster than 108 minutes: 26 seconds \pm 31 minutes: 10 seconds or 127 minutes: 22 seconds \pm 92 minutes: 46 seconds, respectively, in the placebo groups. The recovery times with sugammadex administered at these timepoints may be slightly prolonged compared with the recovery time with sugammadex administered at 1-2 PTCs (the geometric mean recovery time was 2 minutes: 52 seconds in a foreign phase III trial [5.3.5.1.15, Trial 19.4.302]). However, such clinical situations requiring reversal of more profound neuromuscular blockade than the level of blockade at 1-2 PTCs⁴⁴⁾ are very limited, e.g. situations where surgery has been discontinued immediately after administration of a neuromuscular blocking agent or surgery has finished immediately after the administration of a maintenance dose. These recovery times are considered clinically fully acceptable except for situations requiring immediate reversal. The following precaution statements will be included in the package insert: after the return of adequate spontaneous respiration, a dose of 2 mg/kg sugammadex should be administered for the reversal of either rocuronium- or vecuronium-induced blockade; before the return of adequate spontaneous respiration, a dose of 4 mg/kg sugammadex should be administered after any dose of rocuronium and the patient's condition should be monitored closely because recovery from neuromuscular blockade may be delayed; and the efficacy and safety of sugammadex in the reversal of vecuronium-induced neuromuscular blockade before the return of spontaneous respiration have not been established.

PMDA considers as follows:

Although sugammadex should be administered using a neuromuscular monitor wherever possible, the use of sugammadex according to the dosing instructions proposed by the applicant in situations where a neuromuscular monitor can not be used is unlikely to become a clinically relevant problem. The safety of sugammadex in situations where a neuromuscular monitor can not be used needs to be fully investigated after the market launch.

(2) Precaution regarding re-administration of neuromuscular blocking agents after sugammadex administration

PMDA's conclusion that it is difficult to specify a waiting time for re-administration of steroidal neuromuscular blocking agents after sugammadex administration [see Review Report (1) "4.(i).B.(1) Re-administration of neuromuscular blocking agents after sugammadex administration"] was supported at the Expert Discussion. Accordingly, PMDA instructed the

applicant to include a precaution statement in the package insert that, regardless of the type of neuromuscular blocking agent re-administered, the patient's condition should be monitored closely, since it has been suggested that the time to onset of action may be increased for not only steroidal neuromuscular blocking agents that form inclusion complexes with sugammadex, but also a non-steroidal neuromuscular blocking agent, suxamethonium. The applicant modified the statement in the package insert appropriately.

(3) Post-marketing surveillance

PMDA gave the following instructions to the applicant:

- Conduct a post-marketing drug use-results survey with a target sample size of 3000 to investigate the safety of sugammadex, especially regarding hypersensitivity and allergic reactions, bleeding-related adverse events, and re-occurrence of blockade or residual blockade in a broad range of Japanese patients, including patients with impaired renal or hepatic function, geriatric patients, children, and pregnant women/nursing mothers. The survey should also be designed to appropriately investigate the followings: the influences of the neuromuscular blocking agent used (rocuronium bromide or vecuronium bromide), the level of neuromuscular blockade to be reversed by sugammadex, and the use of a neuromuscular monitor on the efficacy and safety of sugammadex; and the details of administration and the safety of sugammadex when sugammadex had to be re-administered or a neuromuscular blocking agent was re-administered after sugammadex administration.
- Conduct a special drug use-results survey concerning the use of sugammadex in situations requiring immediate reversal of neuromuscular blockade following rocuronium administration and design the survey so that information on many patients can be collected as early as possible, e.g. all relevant cases at several medical institutions will be reported.

The applicant accepted the above instructions and explained that the data items, a case report form, etc., will be developed for the surveys so as to investigate the above points. It was also explained that the applicant will conduct a special drug use-results survey on immediate reversal with a target number of patients of 50, who are all retrospectively registered at 5 medical institutions to collect information.

PMDA accepted the above, but considers that the above drug use-results survey and special drug use-results survey should be conducted promptly and the information on the obtained results should be appropriately provided to clinical practice.

(4) Other issues

The proposed brand names have been modified to “Bridion Intravenous 200 mg” and “Bridion Intravenous 500 mg” in terms of risk management.

As a result of the above review, PMDA concludes that the product may be approved after modifying the indication and dosage and administration statements as shown below. The re-examination period is 8 years, neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Indication]

Reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide

[Dosage and administration]

The usual adult dose is 2 mg/kg as sugammadex administered intravenously for routine reversal of shallow neuromuscular blockade (if the reappearance of the second twitch [T_2] in response to train-of-four [TOF] stimulation has been detected with a neuromuscular monitor) and 4 mg/kg as sugammadex administered intravenously for routine reversal of profound neuromuscular blockade (if 1-2 responses to post-tetanic twitch stimulation [1-2 post-tetanic counts (1-2 PTCs)] have been detected with a neuromuscular monitor). If there is a clinical need for immediate reversal following an intubating dose of rocuronium bromide, the usual adult dose is 16 mg/kg as sugammadex administered intravenously at about 3 minutes after the administration of rocuronium bromide.