European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/CHMP/317523/2008

ASSESSMENT REPORT

FOR

Bridion

International Nonproprietary Name: sugammadex

Procedure No. EMEA/H/C/000885

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant N.V. Organon submitted on 21 June 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Bridion, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 16 November 2006.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 24 June 2005, 18 November 2005 and 9 February 2007. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Pirjo Laitinen-Parkkonen** Co-Rapporteur: **Tomas P Salmonson**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 21 June 2007.
- The procedure started on 20 July 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 October 2007.
- During the meeting on 15 November 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 November 2007
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 February 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 April 2008
- During the CHMP meeting on 24 April 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP List of outstanding issues on 29 April 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 12 May 2008
- During the meeting on 27-30 May 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Bridion on 30 May 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 28 May 2008
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 25 July 2008.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

Neuromuscular blocking agents (NMBA) are used as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Reversal agents of neuromuscular blockade are commonly administered at the end of surgery to accelerate the recovery of drug-induced neuromuscular block. Currently available reversal agents are cholinesterase inhibitors such as neostigmine and edrophonium, which inhibit the breakdown of acetylcholine with no effect on the metabolism or elimination of the NMBAs themselves.

However, there is an upper limit to the effect of the current reversal agents; once maximum inhibition of the acetylcholinesterase activity has occurred, neural release of additional acetylcholine becomes the rate-limiting step in restoration of normal muscle function. Consequently, these agents are ineffective in reversing a profound neuromuscular blockade. Additionally, the duration of action of some reversal agents may be shorter than the activity of the NMBAs themselves, leading to reappearance of the NMB, or residual paralysis.

As reversal may not always be completely achieved, patients treated with a cholinesterase inhibitor may still have residual block in the recovery room. Residual block has been reported to occur in 16-64% of patients after single intubating dose of an intermediate-acting non-depolarizing neuromuscular blocking agent. Furthermore, the safety profile of currently available reversal agents are rather unfavourable as cholinesterase inhibitors are associated with a relatively high incidence of cholinergic side effects, including bradycardia, hypotension, salivation, bronchoconstriction and vomiting. Therefore these agents are routinely used in combination with a muscarinic acetylcholine receptor antagonist such atropine or glycopyrrolate to antagonize the muscarinic effects of acetylcholine in the autonomic parasympathetic neuroeffector junctions (e.g., heart). Unfortunately the muscarinic acetylcholine receptor antagonist themselves may cause side effects such as tachycardia, dry mouth, blurred vision.

Bridion is a novel compound Org 25969 (sugammadex), that has been developed for reversal of neuromuscular block induced by the non-depolarizing neuromuscular blockers rocuronium and vecuronium. Org 25969 is a modified γ-cyclodextrin and its mode of action is based on the forming of 1:1 inclusion complexes with rocuronium or vecuronium. Upon intravenous injection complex formation reduces the amount of free neuromuscular blocking agent, leading to a fast reversal of neuromuscular block. It represents an entirely new approach in the management of reversal of neuromuscular blockade. However, sugammadex does not reverse neuromuscular block induced by succinylcholine or benzylisoquinolium compounds.

This unique mechanism of action distinguishes Bridion from the class of anticholinesterase inhibitor reversal agents. Furthermore, select NMBAs (e.g., rocuronium) have been shown to have a higher affinity for Bridion than for the nicotinic receptor, allowing the reversal of a profound NMB to be possible. The mechanism of action of Bridion does not result in stimulation of the cholinergic nervous system. There is no need for concomitant administration of antimuscarinic drugs. Furthermore, due to the removal of the muscle relaxant from its site of action, Bridion is able to reverse even a very profound NMB.

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The applicant submitted a complete and independent application according to Article 8.3 of Directive 2001/83/EC, as amended.

The indication and posology proposed by the applicant for Bridion was for the: *Reversal of neuromuscular blockade induced by rocuronium or vecuronium.*

The recommended clinical doses are 2 and 4 mg/kg for routine reversal and 16 mg/kg for immediate reversal of rocuronium. The 16 mg/kg dose is expected to be used in less than 1% of the treatments.

For routine reversal:
'A dose of 4 mg/kg sugammadex is recommended if recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 3 minutes.

A dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 2 minutes.'

For immediate reversal:
'If there is a clinical need for immediate reversal following administration of rocuronium a dose of 16 mg/kg sugammadex is recommended. When 16 mg/kg sugammadex is administered 3 minutes after a bolus dose of 1.2 mg/kg rocuronium bromide, a median time to recovery of the T_4/T_1 ratio to 0.9 of approximately 1.5 minutes can be expected.

There is no data to recommend the use of sugammadex for immediate reversal following vecuronium induced blockade.'

2.2. Quality aspects

Introduction

Bridion is a sterile solution for intravenous injection, which is presented as 2ml and 5 ml single dose vials containing 100 mg/ml (as sodium salt) of sugammadex as active substance.

Excipients are water for injections, hydrochloric acid (for pH adjustment), or sodium hydroxide (for pH adjustment).

The primary packaging consists in type I glass vials closed with chlorobutyl rubber stoppers held in position with aluminium crimp-caps with flip-off seals.

Active Substance

Sugammadex sodium is a modified γ-cyclodextrin, which contains 8 recurring glucose units each with 5 asymmetric carbon atoms, in total 40 asymmetric carbon atoms for the whole molecule, the original configuration of all asymmetric carbon atoms is preserved during the manufacturing process.

The active substance is a white to off-white octa-sodium salt powder which is highly but reversibly hygroscopic, freely soluble in water, and very slightly- to slightly soluble in polar organic solvents.
The substance shows polymorphism but this is judged to be of no significance for this product.

- Manufacture

Sugamadex is manufactured from γ-cyclodextrin in two chemical reaction steps.

The synthesis is complicated by the fact that it requires the complete conversion of eight identical functional groups per molecule, giving rise to high levels of impurities. Most of these impurities are structurally related γ-cyclodextrins and have physico-chemical characteristics and molecular weights comparable to that of the active substance. This explains why the structurally related impurities are

difficult to fully identify and to remove from the active substance. Major impurities that are structurally related to γ-cyclodextrin were demonstrated to have a comparable pharmacological and toxicological profile to that of sugammadex.

Adequate In-Process Controls are applied during the synthesis of the active substance. Control methods for intermediate products, starting materials and reagents, have been presented.

Batch analysis data of three batches from the manufacturer are presented and confirm consistency and uniformity of the manufacturing process.

- Specification

The active substance specifications for sugammadex are relevant for a substance to be used in intravenous injection as a route of administration and include tests for appearance, colour, visible impurities, identification (HPLC, IR, ICP-AES), assay (HPLC, ICP-AES), impurities (HPLC, ICP-AES), residual solvents (GC), water content (Ph Eur), total aerobic microbial count (Ph Eur), bacterial endotoxins (Ph Eur).

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

- Stability

The primary study made according the ICH stability guideline includes threebatches stored in double LDPE bags in HDPE containers and the real time results are to 24 months. The study at intermediary conditions is completed to 12 months and that in accelerated conditions to 6 months. The results indicate good stability according the parameters studied (appearance, colour, testing for assay and organic impurities, residual ethanol, water content, total aerobic count and endotoxins). Appropriate light sensitivity and forced degradation studies was also made. The solid active substance is not sensitive to light, but quite sensitive to oxidative stress.

The stability results justify the proposed retest period for the active substance.

Medicinal Product

- Pharmaceutical Development

The formulation development has been described and the differences in the composition of the formulations used in the clinical studies have been adequately explained. No overage is used for the manufacture of the solution, but overfill will be used, the target fill volume is slightly higher than the extractable volume. The extractable volume is determined according to Ph.Eur.

All excipients used in the finished product are of pharmacopoeial quality. Sodium hydroxide, sodium chloride, water for injections and nitrogen comply with the requirements of their respective Ph. Eur. monographs.
No excipients are of human or animal origin and there is thus no TSE risk associated with the manufacture of the finished product.

The finished product is filled into glass vials and closed with a rubber stopper and a flip-off aluminium cap. The glass of the vials is of type I and in compliance with the physical and chemical requirements of Ph. Eur. The stoppers are composed of latex free chlorobutyl rubber. The stopper material meets the physical requirements for elastomeric closures for injection preparations of Ph. Eur

- Manufacture of the Product

The manufacturing process includes preparation of the bulk solution, filtration, filling in the vials and terminal sterilization.

Validation studies have been carried out on the sterilisation/depyrogenation of the vials and steam sterilisation of stoppers, filters and aseptic equipment in three production-scale batches and is satisfactory**.** The in process controls are adequate for this pharmaceutical form.

- Product Specification

The finished product specifications include appropriate tests for appearance, colour, identification (HPLC), assay (HPLC), impurities (HPLC), extractable volume (Ph Eur), pH (Ph Eur), osmolality (Ph Eur), clarity (Ph Eur), visible particles (Ph Eur), particulate matter (Ph Eur), bacterial endotoxins (Ph Eur), sterility (Ph Eur).

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control. Impurity limits in the specification are justified by toxicology studies

- Stability of the Product

Stability studies according to ICH guidance have been performed on primary and supportive stability batches. The batches reported can all be considered as pilot-scale batches. 18 months of long term stability data were provided for the primary batches and 36 months of data for the supportive batches. The finished product has been studied at ICH storage conditions 5°C/amb. RH, 25°C/60%RH and 40°C/75%RH as well as in the intermediate conditions 30°C/40%RH and 30°C/75%RH. Results from an ICH photostability study have been submitted and a leaching and container closure integrity study was also conducted. Statistical evaluation of the stability data has been performed for the assay and degradation products in order to support the proposed shelf-life.

As a conclusion from the stability studies, the results indicate satisfactory stability and support the shelf life and conditions stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

Introduction

Org 25969 is a modified γ-cyclodextrin and a novel Selective Relaxant Binding Agent (SRBA); non-clinical data have shown that this compound can reverse a profound aminosteroid-induced NMB.

Pharmacology

- Primary pharmacodynamics

The pharmacodynamics of sugammadex and sugammadex-related cyclodextrins (CDs) have been examined using physicochemical techniques (isothermal titration microcalorimetry), *in vitro* techniques (tissue bath studies), *in vivo* methods (muscle contraction in anaesthetized animals) and side effect profile studies. These studies have shown that Org 25959 is a potent and effective agent for the reversal of neuromuscular blockade induced by the steroidal neuromuscular blocking agents (NMBA) rocuronium, vecuronium and pipecuronium, but is almost ineffective against non-steroidal neuromuscular blocking agents succinylcholine, atracurium, cis-atracurium and mivacurium.

The sugammadex-related cyclodextrins, which are formed during the synthesis process, also show a similar affinity for the steroidal neuromuscular blocking agents. Administration of sugammadex or

Org 259569-related cyclodextrins causes rapid reversal of neuromuscular blockade in *in vitro* and *in vivo* experiments.

- Secondary pharmacodynamics

Due to its mechanism of action, sugammadex has also the potential to bind to other molecules (drugs or endogenous molecules). Isothermal microcalorimetry screening of a large number of molecules has been performed. This included drugs commonly used in anaesthesia, drugs most commonly prescribed and molecules (both steroidal and non-steroidal) acting on steroidal receptors.

Although sugammadex has not been screened for *in vitro* radioligand receptor assays for secondary pharmacological activity, other *in vitro* and *in vivo* assessments have been made to investigate potential off-target effects. None of these studies revealed potential effects related to secondary activity of this drug. It can be concluded therefore that sugammadex does not cause any significant pharmacological effect in *in vitro* and *in vivo* preparations. This appears to be in agreement with results obtained with other cyclodextrin derivatives.

- Safety pharmacology programme

Non-clinical safety pharmacology experiments demonstrate a low risk of secondary pharmacological effects on the vital organ systems such as the central nervous, cardiovascular and respiratory system. In these studies, in general, dose levels and exposures were used that exceeded the normal clinical range.

- Pharmacodynamic drug interactions

An *in vitro* model (mouse hemi-diaphragm) has been developed to study the relationship between microcalorimetric affinity and *in vitro* effect. Two types of interaction can be expected:

  - a molecule can interfere with the interaction between sugammadex and the steroidal neuromuscular blocking agent, and by displacement increase the effect of the NMBA on the neuromuscular junction.
  - a molecule can be encapsulated by sugammadex, thereby reducing the biological effect of that molecule.

Interactions can only be expected when the affinity of a molecule for sugammadex is high and the non- protein bound concentration of this molecule is high. After screening more than 300 compounds using isothermal microcalorimetry, only a few drugs could be identified with a potential interaction: flucloxacillin, fusidic acid, toremifene and hormonal contraceptives. However, this analysis did not take into account that many drugs show a very high affinity to carrier proteins, e.g. steroid-hormone-binding globulin. The underlying mechanism for interactions with these compounds is not clear.

Pharmacokinetics

Most of the non-clinical kinetic data of sugammadex have been collected in conjunction with toxicity or pharmacology studies in the various non-clinical species i.e. rat, guinea pig, rabbit, dog and cat. Levels of sugammadex were determined using validated HPLC-MS assays except for Org 9426 in plasma and urine in a guinea pig pharmacology experiment where an LC-MS/MS method (not GLP validated) was used.

Upon i.v. administration sugammadex rapidly distributes in the extracellular water compartment.. In all species studied, the systemic exposure (AUC and C_0 or C_{max}) generally increased linearly with dose, and no significant differences between the genders were observed. Clearance is predominantly renal, at a rate approximating the GFR. In the plasma and urine HPLC radiochromatograms no qualitative inter-species differences were observed between rat, dog, and man.

The main PK parameters in different species are presented in the table below.

Species	**Rat**		**Rabbit**		**Dog**		**Man**	
Dose	30 $mg \cdot kg^{-1}$		20 $mg \cdot kg^{-1}$		25 $mg \cdot kg^{-1}$		4 $mg \cdot kg^{-1}$	
Gender	M	F	M	F	M	F	M	F
$AUC_{0\text{-}inf}$ ($\mu g \cdot h \cdot mL^{-1}$)	48.7	48.1	n.d.	100.5	134	127	40	40
$NAUC_{inf}$ ($\mu g \cdot h \cdot mL^{-1}$)/($mg \cdot kg^{-1}$)	1.62	1.60	n.d.	5.02	5.17	4.91	10	10
C_0 ($\mu g \cdot mL^{-1}$)	240	145	n.d.	137	252	232	50	50
NC_0 ($\mu g \cdot mL^{-1}$)/($mg \cdot kg^{-1}$)	7.99	4.84	n.d.	6.85	9.73	9.00	12.5	12.5
$t_{1/2}$ (h)	0.4	0.6	n.d.	0.65	0.9	0.9	2	2
CL ($L \cdot kg^{-1} \cdot h^{-1}$)	0.40	0.62	n.d.	0.20	0.19	0.21	0.10	0.10
V ($L \cdot kg^{-1}$)	0.3	0.5	n.d.	0.19	0.25	0.26	0.18	0.18

The metabolism of sugammadex plays no major role in the clearance. The metabolism and interaction especially between Cyp 450 enzymes and sugammadex, related cyclodextrins or impurities was further clarified by the Applicant and the possibility of sugammadex, related cyclodextrins (CDs) or impurities to cause drug-drug interaction based on induction or inhibition of drug metabolizing enzymes was considered to be remote.

The binding of sugammadex to mineralized tissues such as bone and teeth occurs. The extracellular mineral hydroxy apatite could be the binding site, but the binding is reversible. As the sites of bone and teeth growth and remodelling are the preferred sites for disposition, juvenile rats show a higher extent of incorporation as compared to adult or old rats. Furthermore, the presence of rocuronium significantly diminished the binding of sugammadex to the mineralized tissues in the rat. Neonatal exposure to sugammadex via the oral route is assessed to be low.

Toxicology

- Single dose toxicity

Sugammadex was of low acute toxicity following single i.v. administration in the mouse and rat with maximum non-lethal doses at or above 2000 mg/kg. At this dose only mild and very transient clinical signs such as staggered gait were observed, which are most likely associated with the injection of a large volume.

In the acute toxicity studies in the cat and dog, sugammadex was dosed in 3 subdoses of 0.92 or 9.2 $mg.kg^{-1}$ in the absence or presence of a preceding dose of rocuronium. Under these conditions no adverse effects were noted in in-life and terminal parameters. In addition, sugammadex administration alone or combined with rocuronium administration was of low acute toxicity in anaesthetised dogs and cats with maximum non-lethal doses at or above 30 mg/kg.

Sugammadex shows retention in rat bone with a terminal half-life in the range of 70-250 days. Because of the observed retention and long half lives in bone tissue an investigative study was conducted in young adult rats following a single i.v. injection of sugammadex at 2000 mg/kg in order to assess possible effects on bone quality, structure, and turn over. Experimental parameters included morbidity, mortality, body weight, analysis of biochemical bone turnover markers in blood and urine, measurement of femur length and diameter, assessment of bone mineral density and architecture by micro computed tomography (μCT), colour determination of teeth (lower incisors) and bone strength analysis. The observed decrease in trabecular numbers, the related increased trabecular distance, and the decreased strength of trabecular bone when tested in the trabecular bone indentation test might suggest a slight resorptive effect on the femur trabecular bone compartment. However, the

biochemical bone turnover parameters (DPD, CTx, osteocalcin and ALP) are not fully in line with the possible suggestion of a resorptive effect. No significant differences were observed on femur dimensions, cortical bone μCT parameters and the strength assessments in the 3-point bending of femur and femur neck cantilever test (with the exception of a minimal effect on 3-point bending stiffness). The observed effects were limited and most of the effects were reversed 42 days after treatment. Consequently, a wide safety margin is present for potential effects on bone.

The possible slight resorptive effect was explained by the ability of sugammadex to cause a brief surge in plasma parathyroid hormone (PTH) as revealed in a single dose study where effects on PTH levels in serum and urinary calcium excretion were studied in the rat (females only). It was concluded that sugammadex was able to induce a very transient PTH surge which was probably associated with a slight increase in total serum Ca^{2+}. This surge is a normal physiological feedback loop response to a temporary slight decrease of plasma calcium level following the peak exposure after i.v. administration of sugammadex. The mild resorptive effect observed in femur trabecular bone is considered a natural response to a very transient plasma calcium decrease resulting in mobilisation from the physiological calcium reserve in trabecular bone and is not considered as adverse.

- Repeat dose toxicity (with toxicokinetics)

From the 2- and 4-week repeated dose toxicity studies with sugammadex in dog the NOAEL upon repeated dosing for up to 4 weeks is 250 mg.kg-1.

In the 2 and 4-week i.v. toxicity studies with sugammadex in rat the NOEL is determined by microscopic changes in the urinary system. In the kidney cortical tubular cells reabsorption vacuoles are induced (graded as minimal to occasionally moderate) and the urinary bladder foamy cytoplasm is noted in the umbrella cells (upper layer of the urothelium) after repeated dosing at 120 and 500 mg.kg-1.day-1. Both effects are considered to be very mild to mild, as they are not associated with effects on clinical pathology markers of renal or urinary bladder damage in plasma and urine. These effects were probably a result of the extensive urinary excretion and high concentrations of sugammadex in the urine. The NOEL of 500 mg/kg/day in the rat and 250 mg/kg/day (i.e. NOAEL) in the dog as proposed by the Applicant is considered to be acceptable. Exposure margins to the clinical exposure at 16 mg/kg are 6.2 and 6.4, respectively, and at 4 mg/kg, 23.8 and 24.7, respectively.

Minimal to slight effects on body weight gain, food consumption and RBC parameters indicate (very) slight toxicity at the highest dose level in the repeated dose toxicity studies in rats.

Cardiovascular safety of sugammadex has been sufficiently studied. Sugammadex has a low risk of inducting a disturbance in cardiac conductance and in particular on QT interval duration under the intended conditions of use. However significant prolongations in the QT interval in Phase 1-3 studies have been noted (see section on Clinical aspects).

Despite the binding of sugammadex to bone and teeth, in the various non-clinical rat models studied no adverse effect on bone quality, structure and turnover are observed. Moreover, no adverse effects on bone growth, modelling and remodelling have been noted other than those related to the slight non-specific toxicity resulting in a mild degree of growth retardation in juvenile rats upon repeated dosing at the high dose levels. Consequently, a wide safety margin is present for potential effects on bone.

- Genotoxicity

Sugammadex has been tested for mutagenicity and chromosomal aberrations *in vitro*, and for chromosomal aberrations *in vivo* at a single i.v. dose of 1774 mg/kg in the mouse and at repeated i.v. dosing of 500 mg/kg/day in the rat. Exposure margins to the clinical exposure at 16 mg/kg and at 4 mg/kg are 6.2 and 23.8, respectively.

The related cyclodextrines, also contributing to the pharmacological activity, have been tested for mutagenicity and chromosomal aberrations *in vitro*, and for chromosomal aberrations *in vivo* at repeated i.v. dosing of 30 mg/kg/day. A structural alert for the impurity Org 48301 was identified by the Applicant, using DEREK. However, no genotoxic potential was identified for Org 48301 in the

Ame's test or in human peripheral lymphocytes. In conclusion, no genotoxic potential was identified for sugammadex or its related impurities.

- Carcinogenicity

The lack of carcinogenicity studies for sugammadex is accepted since long-term use is not indicated and there are no indications of a genotoxic potential.

- Reproduction Toxicity

Male and female fertility and early embryonic development was studied in the rat. Embryo-fetal development was studied in the rat and the rabbit. Pre-and postnatal developmental studies were performed in the rat.

The fertility and early embryonic development study in Sprague-Dawley rats revealed that the NOAEL of sugammadex for effects on fertility, and early embryonic development exceeds 500mg.kg^{-1}.day^{-1}. In addition, histopathological examination of the male and female reproductive organs in the 4-week rat and dog toxicity studies did not reveal any adverse effects on fertility. Sugammadex induce no reproductive toxic effects.

Based on juvenile rat toxicity studies, the risk for adverse effects on bone growth and development in the paediatric population is considered to be low. The non-clinical observation of incisor discoloration and disturbance of amelogenesis in the juvenile rat revealed a hazard of developmental toxicity to the teeth in the paediatric population. However, the large safety margin indicates that the risk for such an effect in the paediatric population is low given the conditions of clinical use (single dose and in conjunction with an aminosteroidal NMBA).

- Local tolerance

The rabbit is the preferred species for studying local tolerability as it is reported to be the most sensitive species to local effects. The macroscopic observation of a ‘reddish area’ is considered to reflect injection trauma. Because of the microscopic observations at the site of injection, it was considered appropriate to look at the incidence and severity of the findings at a microscopic level. It is concluded that even though a drug-related effect cannot be formally excluded, the mild nature indicates that the sugammadex is tolerated upon accidental intramuscular injection.

In the intended intravenous route good tolerability is observed. It can be concluded that sugammadex is tolerable and that the mild effects observed in muscle are of low relevance to the human situation. In general, there were no major findings in the local tolerance studies which might indicate adverse effects of intravenous administration.

- Other toxicity studies

The exposure of human blood to sugammadex in the absence or presence of rocuronium caused no haemolysis and did not affect osmotic red blood cell fragility.

Photosafety studies were not performed. Low concentrations of sugammadex were detected in the eyes and skin of both albino and pigmented rats to a similar extent, however no specific affinity for melanin is anticipated. The UV spectra of sugammadex exhibits end absorption at about 200 nm, thus the lack of photosafety studies are justified.

The presence of impurities and degradation products did not induce any additional effects in the rat following 2 or 4 weeks repeated i.v. dosing other than those already known from sugammadex and other cyclodextrins. Only mild effects on body weight gain and food consumption was observed. Histopathological findings were limited to slightly increased numbers of foamy alveolar macrophages in the lung, vacuolation of cortical tubular cells in the kidneys, and foamy cytoplasm of the urothelium. These findings were not accompanied with clinical chemistry or urinalysis changes, or progressive pathology. It can be concluded that the specified impurities in drug substance and drug product are toxicologically qualified.

The presence of the different levels of impurities in the different batches of sugammadex, or the degraded drug product did not induce deaths or additional signs of toxicity compared to sugammadex following single i.v. dosing. Minimally increased number of foamy alveolar macrophages in the lungs with complete recovery was observed at 600 mg/kg (degraded sugammadex) and at 2000 mg/kg (degraded and non-degraded sugammadex). Minimal to slight vacuolation of the corticular tubular epithelium in the kidneys with partial recovery was also observed at 600 mg/kg (degraded sugammadex) and at 2000 mg/kg (degraded and non-degraded sugammadex).

Sugammadex is able to slightly stimulate the immune system when administered subcutaneously in the footpad at the highest dose level. A slight increase in white blood cell, WTC count and slight increase in haematocrit in high dose males could also slightly refer to the disturbance of immune system. sugammadex in the absence or presence of rocuronium, induced haemolysis or increased RBC fragility at concentrations around 6 to 7 mg/mL. Sugammadex did not show any immunosuppressive, immunostimulatory, or dermal sensitizing effects in rats or mice in the Plaque Forming Cell Assay, Poplietal Lymph Node Assay, and Local Lymph Node Assay.

Ecotoxicity/environmental risk assessment
An ERA in accordance with Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) was provided comprising of Phase I, Phase II Tier A, and Phase II Tier B consisting of a number of GLP compliant fate and effects studies.

Following the response to the CHMP list of questions (LoQ), the ERA was not considered to be complete and a number of issues such as an additional Daphnia magna reproduction study (in accordance with OECD 211), elaboration of the need for an ERA for the terrestrial compartment, and an updated Phase II, Tier B ERA including an updated PEC sediment calculation needed to be addressed. As a follow-up, the applicant has committed to provide new ERA study protocols and the results, as stated in their letter of undertaking dated 28 May 2008.

2.4. Clinical aspects

Introduction

GCP
Organon claims that all studies were undertaken in accordance with Organon's standard operating procedures, which comply with the principles of Good Clinical Practice.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics (PK)
Sugammadex (Org 25969) 100 mg/ml solution for injection is filled in 2 ml or 5 ml glass vials. Besides sugammadex the formulation contains a related cyclodextrin that is structurally related to sugammadex.

The clinical studies have been performed using 100 mg/ml solution except in four early stage trials where 25 mg/ml strength has been used. In the lower strength formulation sodium chloride has been used as tonicity adjuster. The 100 mg/ml strength is a hypertonic solution where no tonicity adjuster is needed. The results from these studies are considered supportive and the recommendations for labelling are not based on these trials. Besides the strength, pH also has been changed from 7.0 in the early clinical development to 7.5 on the later trials. The pH change is unlikely to affect the efficacy and safety of the product.

The assays that were used for measurement of sugammadex concentrations were validated and found to have appropriate sensitivity.

PK of sugammadex was studied in 15 clinical trials in healthy subjects, patients intended for surgery and in special populations. Sugammadex was administered after the neuromuscular blocking agents

rocuronium (0.6 or 1.2 mg/kg) or vecuronium (0.1 mg/kg), and the concentrations of sugammadex were analysed from plasma and urine samples.

The pharmacokinetic parameters of sugammadex were calculated from the plasma concentration by non-compartmental methods or using population PK modelling. Population PK/PD modelling has been developed to simulate situations not investigated in clinical trials.

The PK of sugammadex is considered to be linear at the therapeutic dose range and concentrations increase dose-proportionally with the dose. Sugammadex is eliminated fast, the half-life being ranging from 66 to 260 minutes, and clearance between 97 and 138 ml/min, which are close to glomerular filtration rate. The drug is eliminated into urine as such. Over 70 % of the radioactive dose is recovered in urine as unchanged drug within 6 hours and over 96 % within 48 hours. Radioactivity is attributed to sugammadex - 100 % in plasma and 95 % in urine, indicating that metabolism of sugammadex is limited.

Comparable PK parameters were observed between the studies. Clearance in anesthetized patients was slightly lower compared to non-anaesthetized subjects.

In vitro studies were performed to determine the extent of binding of [14C]-sugammadex and [3H]-rocuronium to human plasma proteins and human erythrocytes. Sugammadex did not bind to plasma proteins or to erythrocytes, irrespective of the concentration tested. *In vitro* binding of rocuronium was determined in the absence of sugammadex and in the presence of increasing concentrations of sugammadex. The extent of binding of rocuronium to human plasma proteins declined with increasing concentration ratio of sugammadex/rocuronium. Rocuronium, alone or in combination with increasing concentrations of sugammadex, did not bind to erythrocytes of human blood. Sugammadex and rocuronium were efficiently removed from plasma by dialysis when using a high flux membrane.

The applicant has not performed plasma protein binding or erythrocyte binding studies for vecuronium. Nevertheless various citations regarding plasma protein binding in the literature have a given a fair impression on the extent of binding of vecuronium to plasma proteins and erythrocytes, which is low, that no clinically significant safety concerns are expected.

The population PKPD interaction model, including PK for rocuronium and sugammadex, the PK interaction (complex binding) between rocuronium and sugammadex and the PKPD of rocuronium (with and without sugammadex), with respect to Train of Four (TOF), twitch ratio (T_4/T_1) and T_2 twitch height, was developed on the basis of data from healthy volunteers and patients undergoing surgical procedures during maintenance anaesthesia. The model development has been ambitious and great effort has been put into validating the models sufficiently, whereof the most important part is the prediction of data not used in model development (external validation). The further use of the model is for predictions of:
i) the impact of impaired hepatic function,
ii) the effect of capturing interactions,
iii) the effect of displacement interactions,
iv) PK and PD in typical paediatric, elderly or renally impaired subjects.

The PK model for rocuronium was developed and updated on data from more than 200 patients. The model appears to describe and predict observations adequately apart from the elderly, where concentrations were under-predicted. The PK interaction part of the model was developed and updated on data from over 100 patients. The model predicts the total sugammadex concentrations adequately and rocuronium concentrations were predicted reasonably. With respect to the PKPD for rocuronium, the amount of data for model development and update has been limited (n=29). The updated model predicts time to recovery acceptably apart from the highest rocuronium dose (1.2 mg/kg) where time to recovery is predicted to be somewhat shorter than observed. The full PKPD model was initially externally validated in 114 patients with adequate results. The external validation of the updated model performed for 154 patients revealed acceptable predictions in general, but under-predictions of time to recovery were observed after doses of sugammadex, lower than those proposed to be used (2

mg/kg and below). Thus, caution should be observed when the model is used for predictions following low sugammadex doses or at the highest rocuronium dose.

Clarifications were requested in the CHMP LoQ with respect to the model development and the Applicant has updated and redeveloped parts of the PKPD interaction model. However, some issues were identified that may have impact on the predictions from the model, but by combining previous and present knowledge the model predictions are considered acceptable at present. The Applicant will update the model in the future when more paediatric data becomes available, however it is not completely clear how this will be performed. Therefore, and in conjunction with the comments on the newly developed model, it is advised that the full PKPD interaction model should be updated for future predictions; the aim being to develop one model that includes predictions for as many sub-populations as possible. The applicant has committed to present a plan for the update of the model as stated in their letter of undertaking dated 28 May 2008.

- Special populations

PK of sugammadex has been investigated in some special populations. Studies have been performed in elderly (> 65 years, <80 years), in children and in patients with severe renal impairment.

The race effect has been studied between Japanese and Caucasians and no significant race differences are expected between Japanese and Caucasians. Both genders have been included in the studies. Although limited data is available, it seems that the pharmacokinetics of sugammadex in Black or African Americans is similar to Caucasian subjects.

Population PK/PD modelling has been used to evaluate the PK in patients with hepatic impairment and to confirm the findings in children, elderly and renal impairment patients. The modelling is considered acceptable.

Renal impairment

Pharmacokinetic data collected in Phase III trials are available for patients with severe renal impairment (SRI) and elderly patients. No data are available in patients with mild or moderate renal impairment.

In SRI, CL of sugammadex was dramatically decreased (16 times) in comparison with subjects with normal renal function. When sugammadex was administered at reappearance of T_2 there was little effect of SRI on the time to recovery. Furthermore, no alarming effect of SRI was predicted when sugammadex 4 mg/kg was administered at 15 minutes after the rocuronium dose; possibly SRI may result in prolongation of the recovery time by a few minutes compared to normal adults. The predicted effect on recovery times in patients with mild and moderate renal impairment was small. Thus, dose adjustments are not necessary in mild and moderate renal impairment but due to limited clinical data in severe renal impairment, treatment is not recommended in this sub-population. This has been reflected in the SPC, Section 4.2.

The applicant has demonstrated that sugammadex affects rocuronium PK by decreasing clearance and volume of distribution. However the pharmacokinetics of vecuronium in special populations such as patients with mild to moderate renal impairment with concomitant treatment of sugammadex has not been clearly addressed, although it seems this will have no effect on efficacy, as the recovery times are unaffected regardless of age, sex, body weight, race and renal function.

The applicant has committed to investigate the safety of sugammadex in severe renal impaired patients as stated in their letter of undertaking dated 28 May 2008.

Hepatic impairment

No study has been performed in subjects with hepatic impairment since the main elimination pathway for sugammadex is renal excretion. Instead, simulations of the recovery time were performed for patients with normal and impaired hepatic function, covering concomitant treatment of sugammadex and rocuronium. Model predictions indicated the possibility of prolonged time to recovery (by a few minutes) also in impaired hepatic function considering a worst case scenario, i.e. that sugammadex is

affected by hepatic impairment, which is unlikely. Limited clinical data from patients with hepatic impairment do not indicate that time to recovery is prolonged in those patients, however, there are no studies in patients with hepatic impairment and this has been reflected in the SPC, section 4.2.

Furthermore, in the perspective that severe hepatic impairment may result in that other drugs being administered concomitantly are not being cleared as in the normal state, there may be a risk of unexpected drug interactions. Accordingly, sugammadex should be used with great caution in patients with severe hepatic impairment. A cautionary statement has been included in Section 4.2 of the SPC.

The pharmacokinetic data of vecuronium after concomitant administration with sugammadex in patients is limited. However no dose adjustment of sugammadex in mild to moderate patients with hepatic impairment is suggested as vecuronium is eliminated to a lesser extent via liver compared to rocuronium and PK-PD modelling have demonstrated that there will be no need for dose adjustment of rocuronium after concomitant administration of sugammadex to these patients.

- Pharmacokinetic interaction studies

No interaction studies have been performed *in vivo*. The applicant has used PK-PD modelling to predict the possible interactions with sugammadex. The possible interactions based on simulations have been addressed in the SPC.

Since the mechanism of sugammadex is based on complex binding, there is a risk for interactions: sugammadex may bind to other molecules and reduce their effect or the NMBA may be displaced from sugammadex resulting in reduced NMB reversal or reoccurrence of NMB. It appears that the latter type of interactions is most important.

The Applicant has developed a strategy to screen the interaction potential with other compounds. One major foundation of the strategy is assessment of the binding affinity to sugammadex estimated as KA determined by ITC. The other major basis for the strategy is predictions from the PK interaction and the PKPD interaction models. The approach was considered to be acceptable since it was not feasible to perform interactions with all drugs. The model predictions can be reasonably trusted with respect to capturing interactions despite many assumptions in the model predictions. The applicant claims that for capturing interactions, with exceptions of the potential interaction with oral contraceptives, no clinical relevant interaction was expected. In support of this view the Applicant has provided details of anaesthetic regimens used in cases where anaesthetic complications during treatment with sugammadex were observed and no indication of clinically relevant interactions was observed. Predictions on the basis of the PK-PD interaction model have also been performed for extreme scenarios with respect to displacement interactions, and the drugs that were identified with a risk for displacement have been included in the SPC. The proposed and applied interaction strategy will be used to assess interactions with future drugs and this was considered to be an acceptable approach.

Like sugammadex the structurally related cyclodextrin is also eliminated renally unchanged. Possible interactions between the structurally related cyclodextrin and other drugs have been discussed and its interaction potential is expected to be similar to sugammadex.

The CHMP considered that in general, the PK studies have been sufficiently documented and the Applicant has addressed the concerns of the LoQ adequately. A plan for further update of PK-PD model has been requested as a post-authorisation commitment.

Pharmacodynamics

- Mechanism of action

The reversal of rocuronium or vecuronium induced NMB by sugammadex is based on its capability to form an inclusion complex with the NMBA. Upon complexation, the amount of NMBA available to bind to receptors in the neuromuscular junction is reduced, resulting in the reversal of the blockade. This mechanism of action of encapsulation is illustrated by the PK data of rocuronium and vecuronium. An increase in rocuronium or vecuronium plasma concentrations was seen after

administration of sugammadex as a result of redistribution of the NMBA due to complex formation with sugammadex.

- Primary and Secondary pharmacology

The sugammadex clinical pharmacology was studied in seven Phase 1 trials and twelve Phase 2 trials.

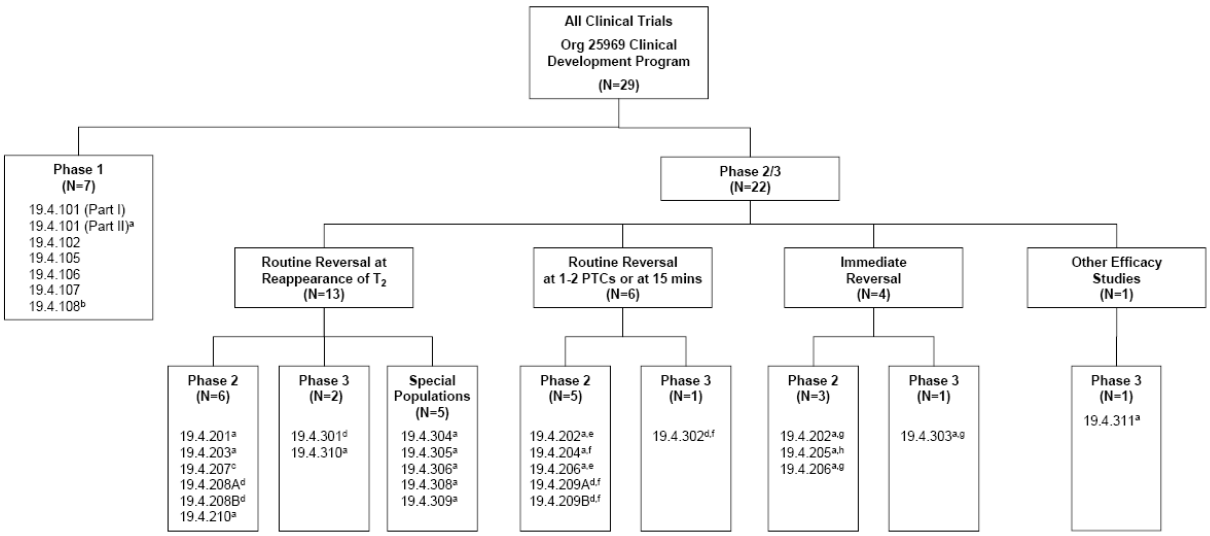
Plasma concentration-time data and data on the efficacy of sugammadex in reversing rocuronium- and vecuronium-induced NMB were collected during the clinical development program in order to develop and validate a population PK-PD modelling describing the mechanism of complex formation between sugammadex and the NMBA. The first version of the model was developed using data from healthy volunteers and from ASA Class 1 and 2 subjects undergoing surgery. The model was later updated to include data from ASA Class 1-3 subjects undergoing surgery. The model describes the depth of a NMB in response to the PK interaction between rocuronium and sugammadex.

Based on the model, after 4 mg.kg-1 of sugammadex administered 15 minutes after 0.6 mg.kg-1 of rocuronium, the typical adult with normal renal function and a body weight of 75 kg was predicted to have a recovery time of 1.5 min. The paediatric population was predicted to have approximately one minute shorter recovery times than adults, and the typical elderly subject was predicted to have a slightly longer or similar recovery time as the typical normal adult. Similar predictions were made following the administration of 2 mg.kg-1 of sugammadex at the reappearance of T2.

The changes in the APTT, PT (inr) and PT in the presence of sugammadex and Org 48302 in *in vitro* tests suggest interference of these drugs with coagulation cascade. Several possible causes for the observed changes in APTT, PT(inr) and PT have been investigated. It is known that anionic cyclodextrin sulfates possess the ability to affect clotting assays and prolong APTT. It is presumed that these sulfated cyclodextrins are able to bind to one or more components of the coagulation cascade and cause inhibition of antithrombin III, factor Xa, and possibly other coagulation factors. This mode of action resembles that of heparins and sulfated polysaccharides, however cyclodextrin sulfates are much less potent. From the non-clinical safety studies there is no impression of impaired clotting (prolonged bleeding times upon toxicokinetic sampling, bruises, microscopical hemorrhages). More importantly, no substantial difference in the adverse event profiles for the sugammadex and placebo group for bleeding complications has been observed so far. As a follow-up, in study 19.4.115, the applicant has committed to investigate the effects of sugammadex on coagulation in volunteers, as stated in their letter of undertaking dated 28 May 2008. There will also be an in vitro part, in which several coagulation tests with different sugammadex concentrations will be tested.

Clinical efficacy

The pivotal efficacy and safety data are derived from the following placebo-controlled Phase II and III studies. In general, the design, conduct, analysis and reporting complied with the relevant guidelines.
The clinical trials are presented in the following figure.



a. Org 25969 administered after rocuronium.
b. Org 25969 administered at the same time as rocuronium or vecuronium.
c. Org 25969 administered after rocuronium, vecuronium, or pancuronium.
d. Org 25969 administered after rocuronium or vecuronium.
e. Routine reversal at 15 minutes.
f. Routine reversal at 1-2 PTCs.
g. Studies 19.4.202 and 19.4.206 investigated immediate reversal at 3 minutes as well as routine reversal at 15 minutes; therefore, these studies are depicted twice in this figure.
h. Immediate reversal at 5 minutes.

In clinical trials investigating the effect of Bridion, neuromuscular blockade and its recovery was measured by acceleromyography (AMG) a technique for recording evoked muscle responses, by using the TOF-Watch® SX a portable acceleromyograph (N.V. Organon, the Netherlands). This device measures the magnitude of contraction of the adductor pollicis muscle in response to four twitches (T_1, T_2, T_3 and T_4) of electrical stimulation of the ulnar nerve. These four twitches are called the Train-Of-Four (TOF). TOF stimulation consists of four supramaximal stimuli of the ulnar nerve (frequency 2 Hz), which provoke 4 twitches of the thumb.

- Dose response studies

Altogether 866 subjects were exposed in Phase 2 trials, and 821 subjects were exposed in Phase 3 trials. Most subjects received either a 2.0 $mg.kg^{-1}$ dose (n=606) or a 4.0 $mg.kg^{-1}$ dose (n=531) - the proposed marketed doses for routine reversal when administered at the reappearance of T_2 or at 1-2 PTCs, respectively. A total of 99 subjects received the 16.0 $mg.kg^{-1}$ dose, which is the proposed marketed dose for immediate reversal at 3 minutes following rocuronium.

Although the total number of patients in total is relatively high, only 99 patients received the higher doses, which are effective in reversing and antagonising a very intense NMB, and furthermore the higher doses were evaluated only in adult patients and not in any of the special patient groups

Twelve clinical trials investigated the dose-response relation of sugammadex administered as reversal agent at various time points after administration of various doses of rocuronium or vecuronium, representing different depths of NMB. Of the twelve trials, four were prospective bridging trials in Japanese and Caucasian subjects (19.4.208A, 19.4.208B, 19.4.209A and 19.4.209B) and one was a Phase 3 trial in paediatric and adult subjects (19.4.306). The trials are grouped below according to the proposed indication.

Studies supporting the dosing in proposed indication: routine reversal at the reappearance of T_2 after rocuronium and vecuronium

Six Phase 2 trials (Trials 19.4.201, 19.4.203, 19.4.207, 19.4.208A, 19.4.208B, and 19.4.306) investigated the efficacy of sugammadex in reversing a rocuronium-induced NMB at the reappearance of T_2.

Based on the calculation of tolerance intervals, it was expected with 97.5% confidence that 90% of subjects will recover to a T_4/T_1 ratio of 0.9 within 3 minutes following a 2.0 $mg.kg^{-1}$ dose of

sugammadex when administered at the reappearance of T_2 following a rocuronium-induced NMB. The choice of this dose was considered to be appropriate regardless of the anaesthetic used (i.e., propofol or sevoflurane; Trials 19.4.208A, 208B, and 210), although sevoflurane appears to prolong spontaneous recovery or recovery following sub-optimal doses of sugammadex, but does not have a clinically relevant effect on the efficacy of 2.0 $mg.kg^{-1}$ sugammadex.

Three Phase 2 trials (Trials 19.4.207, 19.4.208A and 19.4.208B) investigated the efficacy of sugammadex in reversing a vecuronium-induced NMB at the reappearance of T_2.

Pooled results from these trials showed that with a 2.0 $mg.kg^{-1}$ dose of sugammadex recovery of the T_4/T_1 ratio to 0.9 occurs within 2.8 minutes. Doubling the dose to 4.0 $mg.kg^{-1}$ resulted in approximately a 30-second reduction in the mean recovery time.

Based on the calculation of tolerance intervals, it was expected with 97.5% confidence that 90% of subjects will recover to a T_4/T_1 ratio of 0.9 within 5.9 minutes following a 2.0 $mg.kg^{-1}$ dose of sugammadex when administered at the reappearance of T_2 following a vecuronium-induced NMB.

Studies supporting the dosing in proposed indication: routine reversal at 1-2 PTCs and at 15 minutes after rocuronium and vecuronium

Five Phase 2 trials (Trials 19.4.202, 19.4.204, 19.4.206, 19.4.209A and 19.4.209B) investigated the efficacy of sugammadex in reversing a rocuronium-induced NMB at 1-2 PTCs and at 15 minutes following the administration of an intubating dose of rocuronium of 0.6 $mg.kg^{-1}$.

Pooled results from these trials showed a relationship between the dose of sugammadex and recovery of the T_4/T_1 ratio to 0.9. The mean recovery time decreased from 36 minutes following placebo to 1.8 minutes following a dose of 4.0 $mg.kg^{-1}$ of sugammadex. Tolerance intervals calculations indicated that with 97.5% confidence 90% of subjects will recover to a T_4/T_1 ratio of 0.9 within 3.9 minutes following a 4.0 $mg.kg^{-1}$ dose of sugammadex when administered at 1-2 PTCs or 15 minutes following a rocuronium-induced NMB.

Two Phase 2 trials (Trials 19.4.209 a and b) investigated the efficacy of sugammadex in reversing vecuronium-induced NMB at 1-2 PTCs.

Pooled results from these trials showed a relationship between the dose of sugammadex and recovery of the T_4/T_1 ratio to 0.9. The mean recovery time with a dose of 4.0 $mg.kg^{-1}$ was 3.2 minutes. Doubling the dose of sugammadex to 8.0 $mg.kg^{-1}$ resulted in an approximate one-minute reduction in the mean recovery time. Taking into account the fact that only one dosing recommendation is ideal for the use of a reversal agent in a given anaesthesia setting (in this case, reversing a profound block), 4.0 $mg.kg^{-1}$ was chosen for investigation in the Phase 3 program, also for reversing vecuronium-induced NMB at 1-2 PTCs.

Studies supporting the dosing in proposed indication: immediate reversal of a rocuronium induced NMB

Two Phase 2 trials (Trials 19.4.205 and 19.4.206) investigated the efficacy of sugammadex in immediate reversal of rocuronium-induced NMB.

Pooled results from these trials showed a relationship between the dose of sugammadex and recovery of the T_4/T_1 ratio to 0.9. The mean recovery time decreased from 123 minutes following placebo (i.e., spontaneous recovery) to 1.8 minutes following a dose of 12.0 $mg.kg^{-1}$ and 1.6 minutes following a dose of 16.0 $mg.kg^{-1}$. Given the urgency of needing to immediately reverse a NMB (in a cannot-intubate-cannot-ventilate setting), the higher dose of 16.0 $mg.kg^{-1}$ was chosen for investigation in the Phase 3 program.

No trials were conducted to investigate the efficacy of sugammadex in immediate reversal situations following a vecuronium-induced NMB.

- Main studies

The primary efficacy endpoint was time from start of administration of investigational product (IP) to recovery of the T_4/T_1 ratio of 0.9. Inclusion and exclusion criteria were in general similar in the pivotal trials. It has been addressed by the Applicant that blinding for efficacy was not possible in these trials, since the results were available at the measuring device directly and rapid reversal was apparent to the people in the operating room by looking at the patient. Therefore all trials were safety-assessor blinded for the subjective safety assessments.

The efficacy of sugammadex in the three proposed indications, routine reversal at the reappearance of T_2, routine reversal at 1-2 PTCs, and immediate reversal 3 minutes following an intubating dose of rocuronium was evaluated in 4 pivotal Phase 3 trials:

Studies supporting the proposed indication: Routine reversal at the reappearance of T_2 after rocuronium and vecuronium

- Trial 19.4.301 compared sugammadex with neostigmine.
- Trial 19.4.310 compared rocuronium and sugammadex with cisatracurium and neostigmine.

Study supporting the proposed indication: Routine reversal at 1-2 PTCs after rocuronium and vecuronium

- Trial 19.4.302 compared sugammadex with neostigmine

Study supporting the proposed indication: immediate reversal of a rocuronium induced NMB

- Trial 19.4.303 compared reversal of a NMB induced by 1.2 $mg.kg^{-1}$ rocuronium with 16 $mg.kg^{-1}$ sugammadex (administered at 3 minutes following rocuronium) versus spontaneous recovery from 1.0 $mg.kg^{-1}$ succinylcholine.

Studies supporting the proposed indication: Routine reversal at the reappearance of T_2 after rocuronium and vecuronium

- **Trial 19.4.301** compared sugammadex with neostigmine.

Table 57 Overview of clinical efficacy trials

Protocol no.[1] No. of centers (country) Trial status (start–end dates)	Trial objectives	Trial design	Trial & control drugs Dosage form (product ID/batch) Dose, route, regimen, & duration	Diagnosis (inclusion criteria)	Enrolled/treated/ completed, by trial arm	Gender[a] M/F	Age (yr)[a] Mean/median/ range	Primary endpoint
19.4.301 13 centers (AT, BE, DE, ES, GB, IT, SE) Complete (November 2005 – March 2006)	To demonstrate faster recovery from rocuronium or vecuronium after reversal at reappearance of T_2 by 2.0 mg/kg Org 25969 compared to 50 µg/kg neostigmine, and to evaluate the safety of 2.0 mg/kg Org 25969 and 50 µg/kg neostigmine	Multi-center, randomized, parallel group, comparative, active controlled safety-assessor blinded, pivotal trial	Org 25969: 100 mg/mL: (CY184). Dose 2.0 mg/kg iv, single dose Rocuronium bromide: 10 mg/mL: (CX204). Dose 0.6 mg/kg + maintenance doses, iv Vecuronium bromide: 2 mg/mL (CY197). Dose 0.1 mg/kg + maintenance doses, iv Water for injection: 10 mL ampoules (CZ020). Neostigmine/glycopyrrolate (premix): 2.5 mg/mL neostigmine and 0.5 mg/mL glycopyrrolate (CZ015). Dose 50 µg/kg iv, single dose	ASA class 1 to 4, aged ≥ 18, scheduled for surgical procedure in supine position with a general anesthesia with the use of rocuronium or vecuronium	Rocuronium + Org 25969: 49/48/47 Rocuronium + neostigmine: 49/48/47 Vecuronium + Org 25969: 51/48/47 Vecuronium + neostigmine 49/45/44	Rocuronium + Org 25969: 31/17 Rocuronium + neostigmine: 24/24 Vecuronium + Org 25969: 26/22 Vecuronium + neostigmine 21/24	Rocuronium + Org 25969: 51/50/20-83 Rocuronium + neostigmine: 48/51/18-73 Vecuronium + Org 25969: 49/47/20-81 Vecuronium + neostigmine 50/51/21-81	Time from start administration of IP to recovery of the T_4/T_1 ratio to 0.9

METHODS

Study Participants
See table above.

Treatments
Subjects were to receive rocuronium or vecuronium in randomized order with single and maintenance (if applicable) dosing according to local treatment practice. After the last dose of rocuronium or vecuronium, at reappearance of T2, 2.0 $mg.kg^{-1}$ sugammadex or 50 $\mu g.kg^{-1}$ neostigmine was to be administered in randomized order. All patients received propofol, sevoflurane and some opioid analgesic. At the time of administration of sugammadex or neostigmine, the recommended concentration of sevoflurane was to be < 1.5 MAC.

Objectives
The **primary** objective was to demonstrate faster recovery from a neuromuscular block induced by vecuronium or rocuronium after reversal at reappearance of T2 by 2.0 $mg.kg^{-1}$ sugammadex compared to 50 $\mu g.kg^{-1}$ neostigmine.

The **secondary** objective was to evaluate the safety of a single dose of 2.0 mg.kg-1 sugammadex and 50 μg.kg-1 neostigmine administered in adult subjects with ASA 1-3.

Outcomes/endpoints
The primary efficacy variable was the time from start of administration of sugammadex /neostigmine to recovery of the T4/T1 ratio to 0.9 (see Table above).

Sample size
Simulations were performed to estimate the sample size based on the results of previous trials. They indicated that if a difference of at least 5 minutes in the mean recovery times between sugammadex and neostigmine had to be detected with 95% probability, 46 subjects should be enrolled for each of the two sugammadex groups and each of the two neostigmine groups. Taking into account that about 5% of the subjects might drop out from the ITT (intent-to-treat) evaluation, the sample size should be 49 for the sugammadex and neostigmine groups: i.e. 196 subjects in total.

Randomisation
The enrolled subjects received a randomization number via a central randomization system, which was to identify their treatment.

Blinding (masking)
The person who was to prepare and administer, if applicable the syringes with IP was to be unblinded for that subject. The investigators performing safety assessments during anaesthesia should have been kept blind as long as possible.

Statistical methods
Demographic, baseline, exposure and safety data were summarized by treatment group. Times from start of administration of the IP to recovery of the T4/T1 ratio to 0.9, 0.8 and 0.7 were analyzed using a two-way ANOVA model. The logarithm of the recovery time was taken as response variable, and trial site and treatment group were the factors of the model. For the ITT population two evaluations were performed: one for which missing recovery times were imputed and one that used only the available recovery times. Statistical testing for differences between the two treatment groups was done one-sided, at a significance level of 2.5%.

RESULTS

Participant flow

Study 19.4.301

Table Number of subjects in the different subject data sets, within and across treatment group, rocuronium group

Subject data set	Treatment group		Total (n)
	Org 25969 (n)	Neostigmine (n)	
ASR	49	49	98
AST	48	48	96
ITT	48	48	96
PP	44	47	91

Data were taken from Appendix F, Table 1.5-R.A

Table Number of subjects in the different subject data sets, within and across treatment group, vecuronium group

Subject data set	Treatment group		Total (n)
	Org 25969 (n)	Neostigmine (n)	
ASR	51	49	100
AST	48	45	93
ITT	48	45	93
PP	45	41	86

Data were taken from Appendix F, Table 1.5-V.A
ASR - All subjects randomised, AST - All subjects treated, ITT - Intent to treat, PP - Per protocol

Recruitment
Rocuronium group
In total 98 subjects were enrolled and all were randomly allocated to either sugammadex or neostigmine to reverse neuromuscular block induced by rocuronium.

Vecuronium group
In total 100 subjects were enrolled and all were randomly allocated to sugammadex or neostigmine to reverse neuromuscular block induced by vecuronium.

Conduct of the study
All subjects in the AST group received an intubating dose of rocuronium. Thirty four subjects received at least one maintenance dose of rocuronium: 15 in the sugammadex group and 19 in the neostigmine group. The median number of maintenance doses was three, and the individual number of maintenance doses ranged from one to nine.

All subjects in the AST group received an intubating dose of vecuronium. Thirty three subjects received at least one maintenance dose of vecuronium: 20 subjects in the sugammadex group and 13 subjects in the neostigmine group. The median number of maintenance doses was two, and the individual number of maintenance doses ranged from one to 15.

Baseline data
Rocuronium group
In total 41 females and 55 males ASA physical status 1-3 patients were treated with the IP. The mean (range) age of these subjects was 50 (18 - 83) years. The majority (94 out of 96) of these subjects were Caucasian. No differences were observed between the two treatment groups with respect to age: the mean (SD) age was 51 (16) years in sugammadex group and 48 (14) in the neostigmine group. The

same holds for the body weight of the subjects: mean (SD) values were 73 (14) kg in the sugammadex group and 76 (15) kg in the neostigmine group. More males (65%) were enrolled in the sugammadex group as compared to the neostigmine group (50%). All subjects received their assigned dose of sugammadex or neostigmine.

Vecuronium group
In total 46 females and 47 males ASA physical status 1-3 patients were treated with the IP. The mean (range) age of the subjects in the AST group was 49 (20 - 81) years. All subjects were Caucasian.

There was no differences between the two treatment groups with respect to age: the mean (SD) age was 49 (16) years in sugammadex group and 50 (15) years in the neostigmine group, or for the body weight of the patients: mean (SD) values were 81 (19) kg in the sugammadex group and 76 (13) kg in the neostigmine group. More males (54%) were enrolled in the sugammadex group as compared to the neostigmine group (47%). All subjects received their assigned dose of sugammadex or neostigmine.

Numbers analysed
Rocuronium group
Two randomized subjects did not receive a dose of sugammadex or neostigmine, resulting in 96 subjects in the AST group. All subjects in the AST group had at least one efficacy assessment and thus the ITT group consisted of 96 subjects. Major protocol violations were seen in five subjects, and thus the per protocol (PP) group consisted of 91 subjects.

Vecuronium group
Seven randomized subjects did not receive a dose of sugammadex or neostigmine resulting in 93 subjects in the AST group. All subjects in the AST group had at least one efficacy assessment and thus the ITT group consisted of 93 subjects. Major protocol violations were seen in seven subjects thus the PP group consisted of 86 subjects.

Outcomes and estimation

Table Summary of the time (min) from start of administration of sugammadex or neostigmine administered at **reappearance of T_2 following rocuronium** to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

	Trial 19.4.301[b]	
	Rocuronium + **sugammadex** (2.0 $mg.kg^{-1}$)	**Rocuronium +** **Neostigmine** (50 μg.kg-1)
n	48	48
Geometric Mean	1.5	18.5
95% CI	1.3 – 1.7	14.3 – 23.9
Median	1.4	17.6
Min. – max.	0.9 – 5.4	3.7 – 106.9
p-value[a]	<0.001	

[a] P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.
[b] Anaesthetic regimen included induction with propofol and maintenance with sevoflurane.

It was estimated that the time from administration of sugammadex to recovery of the T4/T1 ratio to 0.9 was 12.4 times faster compared to the time from administration of neostigmine to recovery of the T4/T1 ratio to 0.9 following rocuronium. The lower limit of the corresponding 97.5% CI was 9.4.

Table Summary of the time (min) from start of administration of sugammadex or neostigmine administered at **reappearance of T_2 following vecuronium** to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

	Trial 19.4.301[b]	
	Vecuronium + **sugammadex** (2.0 $mg.kg^{-1}$)	**Vecuronium** + **Neostigmine** (50 $\mu g.kg^{-1}$)
n	48	45
Geometric Mean	2.8	16.8
95% CI	2.3 – 3.4	12.9 – 21.9
Median	2.1	18.9
Min. – max.	1.2 – 64.2	2.9 – 76.2
p-value[a]	<0.001	

[a] P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.
[b] Anaesthetic regimen included induction with propofol and maintenance with sevoflurane.

It was estimated that the time from administration of sugammadex to recovery of the T4/T1 ratio to 0.9 was 6.6 times faster compared to the time from administration of neostigmine to recovery of the T4/T1 ratio to 0.9 following vecuronium. The lower limit of the corresponding one-sided 97.5% CI was 4.7.

Compared to neostigmine, sugammadex provided significantly faster recovery of the T4/T1 ratio to 0.9 both after rocuronium and vecuronium induced NMB. The recovery was faster after rocuronium than that after vecuronium, 1.5 min vs. 2.8. min. Moreover as could be expected, based on the Phase 2 studies at the dose of 2.0 $mg.kg^{-1}$ of sugammadex, there was a high inter-individual variation in the recovery times after vecuronium induced NMB.

Ancillary analyses
The following table presents the times from the start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9 for subjects who received only an intubating dose of rocuronium, and for subjects who received an intubating dose and at least one maintenance dose of rocuronium.

Table **Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 for subjects who received an intubating dose only and those who received at least one maintenance dose, rocuronium group (ITT group)**

		Intubating dose only	**Intubating dose and maintenance dose(s)**
Including imputed data	n	33	15
	Geometric mean	1:28	1:31
	Mean (SD)	1:34 (0:47)	1:42 (0:56)
	Median	1:23	1:25
	Min. – max.	0:56 – 5:25	0:55 – 4:11
Complete cases	n	33	14
	Geometric mean	1:28	1:28
	Mean (SD)	1:34 (0:47)	1:38 (0:56)
	Median	1:23	1:18
	Min. – max.	0:56 – 5:25	0:55 – 4:11

Data were taken from Appendix F, Table 6.1-R.C.1

These times indicate that reversal of neuromuscular block by sugammadex is not affected by the last dose of rocuronium administered: intubating dose (0.6 mg.kg-1) and maintenance dose (0.10 to 0.20 mg.kg-1).

The table below presents the times from administration of sugammadex to recovery of the T4/T1 ratio to 0.9 for subjects who received only an intubating dose of vecuronium, and for subjects who received an intubating dose and at least one maintenance dose of vecuronium.

Table **Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 for subjects who received an intubating dose only and those who received at least one maintenance dose, vecuronium group (ITT group)**

		Intubating dose only	Intubating dose and maintenance dose(s)
Including imputed data	n	28	20
	Geometric mean	2:21	3:35
	Mean (SD)	4:28 (11:46)	4:28 (4:02)
	Median	1:56	3:26
	Min. – max.	1:12 – 64:12	1:41 – 19:47
Complete cases	n	27	19
	Geometric mean	2:15	3:27
	Mean (SD)	4:22 (11:59)	4:20 (4:06)
	Median	1:56	3:26
	Min. – max.	1:12 – 64:12	1:41 – 19:47

Data were taken from Appendix F, Table 6.1-V.C.1

These data indicate that the reversal of NMB by sugammadex is similar after a single or repeated (maintenance) doses of rocuronium. On the contrary, recovery of NMB induced by repeated doses of vecuronium is two-times longer that that after a single dose of vecuronium.

Study supporting the proposed indication: Routine reversal at the reappearance of T_2 after rocuronium and vecuronium

- **Trial 19.4.310** compared rocuronium and sugammadex with cisatracurium and neostigmine.

Table 57 **Overview of clinical efficacy trials**

Protocol no.[1] No. of centers (country) Trial status (start–end dates)	Trial objectives	Trial design	Trial & control drugs Dosage form (product ID/batch) Dose, route, regimen, & duration	Diagnosis (inclusion criteria)	Enrolled/treated/ completed, by trial arm	Gender[a] M/F	Age (yr)[a] Mean/median/ range	Primary endpoint
19.4.310 8 centers (ES, FR, GB, IT) Complete (November 2005 - May 2006)	To show a faster recovery with Org 25969 after rocuronium as compared to neostigmine after cisatracurium when administered at reappearance of T_2, to evaluate the safety of a single dose of 2.0 mg/kg Org 25969 and 50 µg/kg neostigmine administered in adult subjects and to show a faster onset of neuromuscular blockade after 0.6 mg/kg rocuronium as compared to 0.15 mg/kg cisatracurium	Multi-center, randomized, safety-assessor blinded, parallel group, active controlled comparative trial.	Org 25969:100 mg/mL: (CY039). Dose 2.0 mg/kg iv single dose. Rocuronium bromide: 10 mg/mL (CX204). Dose 0.6 mg/kg + maintenance doses, iv Cisatracurium besilate 2 mg/mL (CZ098 and CZ141) Dose 0.15 mg/kg + maintenance doses, iv Neostigmine/glycopyrrolate (premix): 2.5 mg/mL neostigmine and 0.5 mg/mL glycopyrrolate) (CZ015) Dose 50 µg/kg iv, single dose	Subjects of ASA class 1 to 4, above or equal to the age of 18 years; scheduled for surgical procedure under general anesthesia requiring neuromuscular relaxation with the use of rocuronium or cisatracurium; scheduled for surgical procedures in supine position	Rocuronium+ Org 25969: 40/34/33 Cisatracurium+ neostigmine: 44/39/39	Rocuronium+ Org 25969: 14/20 Cisatracurium+ neostigmine: 23/16	Rocuronium+ Org 25969: 49/48/23-76 Cisatracurium+ neostigmine: 42/40/22-69	Time from start administration of IP to recovery of the T_4/T_1 ratio to 0.9

METHODS

Study Participants
See table above.

Treatments
Subjects were to receive either a bolus dose of 0.6 mg.kg^{-1} rocuronium or a bolus dose of 0.15 mg.kg^{-1} cisatracurium in randomized order, with maximally two maintenance doses (if applicable). After the last dose of rocuronium, at reappearance of T2, 2.0 mg.kg^{-1} sugammadex was to be administered, and after the last dose of cisatracurium, at reappearance of T2, 50µg.kg^{-1} neostigmine was to be administered, in randomized order. All patients received propofol and some opioid analgesic. The groups were comparable by the baseline data.

Objectives
The **primary** objective was to show a faster recovery of neuromuscular block with sugammadex after rocuronium as compared to neostigmine after cisatracurium when administered at reappearance of T2.

The **secondary** objectives were to evaluate the safety of a single dose of 2.0 mg.kg-1 sugammadex and 50 µg.kg-1 neostigmine administered in adult subjects and to show a faster onset of neuromuscular block after 0.6 mg.kg-1 rocuronium as compared to 0.15 mg.kg-1 cisatracurium.

Both objectives are relevant for routine clinical use. However, sugammadex and neostigmine were administered to patients who had levels of NMB that were deeper than usual clinical practice.

Outcomes/endpoints
The primary efficacy variable was the time from start of administration of sugammadex /neostigmine to recovery of the T4/T1 ratio to 0.9 (see Table above).

Sample size
Simulations were performed to estimate the sample size based on the results of previous trials. Simulations indicated that if a SD of 1.5 minutes was assumed in the sugammadex group and of 5.5 minutes in the neostigmine group, and if a difference of at least three minutes in the mean recovery times between sugammadex and neostigmine had to be detected with 90% probability, 40 subjects should be enrolled for the sugammadex and the neostigmine groups. Taking into account that about 5% of the subjects might have dropped out from the ITT evaluation, the sample size should be 42 for the sugammadex and neostigmine group: i.e. 84 subjects in total.

Randomisation
As for Trial 19.4.301 (see above).

Blinding (masking)
As for Trial 19.4.301 (see above).

Statistical methods
As for Trial 19.4.301 (see above).

RESULTS

Participant flow
The table below presents an overview of the number of subjects within the different subject data sets by treatment group and overall.

Table Number of subjects in the different subject data sets, within and across treatment group

Subject data set	Treatment group		Total (n)
	roc/Org 25969 (n)	cis/Neostigmine (n)	
ASR	40	44	84
AST	34	39	73
ITT	34	39	73
PP	30	35	65

ASR - All subjects randomised, AST - All subjects treated, ITT - Intent to treat, PP - Per protocol

Recruitment
In total 84 subjects were enrolled and randomly allocated to receive rocuronium/sugammadex or cisatracurium/neostigmine.

Conduct of the study
Eleven randomized subjects did not receive a dose of sugammadex or neostigmine, resulting in 73 subjects in the AST group. All subjects in the AST group received an intubating dose of rocuronium or cisatracurium. Sixteen subjects in the roc/sugammadex group and 14 subjects in the cis/neostigmine group received at least one maintenance dose. Median number of maintenance doses was two in the roc/sugammadex group and one in the cis/neostigmine group, and the maximum individual number of maintenance doses was two in both groups, which was the maximum allowed according to the protocol.

Baseline data
In total 36 females and 37 males ASA physical status 1-3 patients were treated with the IP. The mean (range) age of these subjects was 45 (22 - 76) years. The majority (72 out of 73) of these subjects were Caucasian.

The mean age was higher in the roc/sugammadex group compared to the cis/neostigmine group, i.e. 49 versus 42 years respectively. The percentage of women in the roc/sugammadex group was somewhat higher, i.e. 59% versus 41% in the cis/neostigmine group. The mean weight and height in the roc/sugammadex group was somewhat lower compared to the cis/neostigmine group (72 kg and 166 cm in the roc/sugammadex group and 78 kg and 172 cm in the cis/neostigmine group, respectively). The percentage of subjects in the roc/sugammadex group with ASA class 2 or 3 was higher compared to the cis/neostigmine group; 62% (53% in ASA class 2 plus 9% in ASA class 3) versus 46% (all in ASA class 2), respectively.

Numbers analysed
Eleven randomized subjects did not receive a dose of sugammadex or neostigmine, resulting in 73 subjects in the AST group. All subjects in the AST group had at least one efficacy assessment and thus the ITT group consisted of 73 subjects. Major protocol violations were seen in eight subjects, and thus the PP group consisted of 65 subjects

Outcomes and estimation

Table Summary of the time (min) from start of administration of Sugammadex or neostigmine administered at **reappearance of T_2 following rocuronium or cisatracurium,** respectively, to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

	Trial 19.4.310[b]	
	Rocuronium + **sugammadex** (2.0 $mg.kg^{-1}$)	**Cisatracurium** + **Neostigmine** (50 $\mu g.kg^{-1}$)
n	34	39
Geometric Mean	2.0	8.8
95% CI	1.7 – 2.4	7.4 – 10.4
Median	1.9	7.2
Min. – max.	0.7 – 6.4	4.2 – 28.2
p-value[a]	<0.001	

[a] P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.
[b] Anaesthetic regimen included induction and maintenance with propofol.

Primary efficacy variable
The geometric mean time from administration of sugammadex or neostigmine to recovery of the T4/T1 ratio to 0.9 was 2 min:02 sec and 8 min:46 sec, respectively, including imputed data. The time from administration of sugammadex to recovery of the T4/T1 ratio to 0.9 was estimated to be 4.3 times faster compared to the time from administration of neostigmine to recovery of the T4/T1 ratio to 0.9. The lower limit of the corresponding 95% CI was 3.4 times faster.

Exploratory analyses suggested that reversal of neuromuscular blockade by sugammadex did not differ between subjects who received only an intubating dose of rocuronium compared to subjects who received at least one maintenance dose as well.

Recovery of deep NMB was significantly faster after rocuronium block reversed with sugammadex than that of cisatracurium + neostigmine.

Ancillary analyses

Table **Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 for subjects who received an intubating dose only and those who received an intubating dose and at least one maintenance dose (ITT group)**

		Intubating dose only	**Intubating dose and maintenance dose(s)**
Including imputed data	n	18	16
	Geometric mean	2:10	1:53
	Mean (SD)	2:33 (1:34)	2:02 (0:58)
	Median	2:16	1:49
	Min. – max.	0:41 - 6:24	1:07 - 5:07
Complete cases	n	17	15
	Geometric mean	2:04	1:45
	Mean (SD)	2:24 (1:28)	1:50 (0:32)
	Median	2:11	1:43
	Min. – max.	0:41 - 6:24	1:07 - 3:05

Data were taken from Appendix F, Table 6.1-C

These times suggest that reversal of neuromuscular blockade by sugammadex is not affected by the last dose of rocuronium administered: intubating dose (0.6 mg.kg-1) and intubating dose and at least one maintenance dose (0.10 to 0.20 mg.kg-1).

Study supporting the proposed indication: Routine reversal at 1-2 PTCs after rocuronium and vecuronium

- **Trial 19.4.302** compared sugammadex with neostigmine

Table 57 Overview of clinical efficacy trials

Protocol no.[1] No. of centers (country) Trial status (start–end dates)	Trial objectives	Trial design	Trial & control drugs Dosage form (product ID/batch) Dose, route, regimen, & duration	Diagnosis (inclusion criteria)	Enrolled/treated/ completed, by trial arm	Gender[a] M/F	Age (yr)[a] Mean/median/ range	Primary endpoint
19.4.302 8 centers (USA) Complete (November 2005 – November 2006)	To demonstrate faster recovery from rocuronium or vecuronium after reversal at a block of 1-2 PTCs by 4.0 mg/kg Org 25969 compared with 70 µg/kg neostigmine and to evaluate the safety of a single dose of 4.0 mg/kg Org 25969 and 70 µg/kg neostigmine	Multicenter, randomized, parallel group, comparative, active controlled, safety-assessor blinded trial	Org 25969: 100 mg/mL (CY039 and CZ180). Dose 4.0 mg/kg iv, single dose Rocuronium bromide: 10 mg/mL (1910804592, 1336901115 and 1258902582). Dose 0.6 mg/kg + maintenance doses, iv Vecuronium bromide: 1 mg/kg (697029). Dose 0.1 mg/kg + maintenance doses, iv Sterile Water for Injection: 20 mL vials (4493). Neostigmine: 1 mg/mL (04L117 and 105020). Dose 70 µg/kg iv, single dose Glycopyrrolate: 0.2 mg/mL (094093). Dose 14 µg/kg iv, single dose	Aged 18 years old or older, ASA Class 1 to 4, scheduled to undergo an elective surgical procedure under general anesthesia in the supine position requiring the use of rocuronium or vecuronium for endotracheal intubation and maintenance of neuromuscular blockade	Rocuronium + Org 25969: 48/37/37 Rocuronium + neostigmine: 40/38/37 Vecuronium + Org 25969: 52/46/46 Vecuronium + neostigmine 42/36/35	Rocuronium + Org 25969: 16/21 Rocuronium + neostigmine: 17/21 Vecuronium + Org 25969: 17/29 Vecuronium + neostigmine 21/15	Rocuronium + Org 25969: 52/51/19-85 Rocuronium + neostigmine: 54/54/30-73 Vecuronium + Org 25969: 50/51/25-78 Vecuronium + neostigmine 57/60/29-77	Time from start administration of IP to recovery of the T_4/T_1 ratio to 0.9

METHODS

Study Participants

See table above.

Treatments

According to the randomized treatment group, subjects were to receive an intubating dose of either 0.6 mg.kg-1 rocuronium or 0.1 mg.kg-1 vecuronium, and neuromuscular block was to be maintained with either a bolus dose(s) of 0.15 mg.kg-1 rocuronium or a bolus dose(s) of 0.015 mg.kg-1 vecuronium. After the last dose of rocuronium or vecuronium, subjects were to be reversed at 1-2 PTCs with a single bolus dose of either 4.0 mg.kg-1 sugammadex or 70 µg.kg-1 neostigmine (total dose was not to exceed 5 mg) plus 14 µg.kg-1 glycopyrrolate according to their randomized treatment group.

Objectives

The **primary** objective was to:

- to demonstrate faster recovery from a neuromuscular block induced by rocuronium after reversal at a block of 1-2 PTCs by 4.0 mg.kg-1 sugammadex compared with 70 mcg.kg-1 neostigmine.
- to demonstrate faster recovery from a neuromuscular block induced by vecuronium after reversal at a block of 1-2 PTCs by 4.0 mg.kg-1 sugammadex compared with 70 mcg.kg-1 neostigmine.

The **secondary** objective was to evaluate the safety of a single dose of 4.0 mg.kg-1 Bridion and 70 mcg.kg-1 neostigmine administered in adult subjects.

Outcomes/endpoints

The primary efficacy variable was the time from start of administration of sugammadex/neostigmine to recovery of the T4/T1 ratio to 0.9. The efficacy was based on evaluation of neuromuscular functioning as measured by acceleromyography (TOF-Watch and clinical signs of recovery).

Sample size

For the sample size calculations, a SD of the recovery time of 1.5 min after sugammadex was to be assumed while for the SD after neostigmine (under maintenance anaesthesia with sevoflurane) a range from 5.0-15.0 min was to be assumed. Simulations indicated that if 30 subjects per treatment group were to participate with data to the statistical evaluation and the SD in the sugammadex group was 1.5 min and in the neostigmine group was 7.0 min, then existing differences of at least 5 min would have been detected with about 95% probability.

Taking into account that about 5% of the subjects might have dropped out from the Intent-to-Treat evaluation, the sample size should have been 32 for each the sugammadex and neostigmine groups: i.e., 128 subjects in total. In order to evenly distribute the enrolment over the nine trial sites, the sample size was 36 per treatment group, i.e., 144 subjects in total. In this way, each investigational site was to enrol 4 subjects per treatment group, i.e., 16 subjects in total.

Randomisation
The subject allocation numbers were to be assigned to subjects in sequential order of their enrolment in the trial. At each trial centre, the first subject enrolled received the first site subject allocation number (the lowest) and the assigned treatment group in the Randomization Schedule.

Blinding (masking)
The person who prepared the medication was not to perform any subjective safety assessments for any of the subjects, and the safety assessor was not allowed to witness the preparation of the IP.

Statistical methods
Reporting of the data was done for each of the two NMBAs (rocuronium and vecuronium) separately. Demographic, baseline, exposure, and safety were summarized by treatment group. Times from start of administration of IP (sugammadex and neostigmine) to recovery of the T4/T1 ratio to 0.9, 0.8 and 0.7 were analyzed using a two-way ANOVA model. The logarithm of the recovery time was taken as response variable, and trial site and treatment group were the factors of the model. For the Intent-to-Treat population two evaluations were performed: one for which missing recovery times were imputed and one that used only the available recovery times. Statistical testing for differences between the two treatment groups was done one-sided, at a significant level of 2.335% (adjusted after the interim analysis). Clinical signs of recovery were summarized by treatment group only.

RESULTS
Participant flow

Rocuronium group
The number of subjects in each subject data set, within and across treatment group is presented below in the tables below.

Table Number of subjects in each subject data set, within and across treatment group, rocuronium group

Subject data set	Treatment group		Total
	Org 25969 (n)	Neostigmine (n)	(n)
All-Subjects-Randomized Group	48	40	88
All-Subjects-Treated Group [a)]	37	38	75
Intent-to-Treat Group [b)]	37	37	74
Per-Protocol Group	32	31	63

Data were taken from Appendix F, Table 1.5-R.A
a) The All-Subjects-Treated Group was based on actual treatment received. One subject randomized to the vecuronium + Org 25969 group was treated with rocuronium + neostigmine.
b) The Intent-to-Treat Group was based on the randomized treatment group.

Vecuronium group
The number of subjects in each subject data set, within and across treatment group is presented below.

Table Number of subjects in the different subject data sets, within and across treatment group, vecuronium group

Subject data set	Treatment group		Total (n)
	Org 25969 (n)	Neostigmine (n)	
All-Subjects-Randomized Group	52	42	94
All-Subjects-Treated Group [a)]	46	36	82
Intent-to-Treat Group [b)]	47	36	83
Per-Protocol Group	38	30	68

Data were taken from Appendix F, Table 1.5-V.A
a) The All-Subjects-Treated Group was based on actual treatment received. One subject randomized to the vecuronium + Org 25969 group was treated with rocuronium + neostigmine.
b) The Intent-to-Treat Group was based on the randomized treatment group.

Recruitment
Rocuronium group
A total of 88 subjects were randomized to a treatment group, including 48 subjects in the sugammadex group and 40 subjects in the neostigmine group.

Vecuronium group
A total of 94 subjects were randomized to a treatment group, including 52 in the sugammadex group and 42 in the neostigmine group.

Conduct of the study
Rocuronium group
Thirty seven patients were treated with rocuronium and sugammadex and 37 patients were treated with rocuronium and neostigmine, and all completed the trial. All subjects received an intubating dose of rocuronium. A maintenance dose of rocuronium was not administered to 2 subjects in the sugammadex group and 3 subjects in the neostigmine group. For the subjects who received maintenance doses of rocuronium, the median dose of 0.15 mg.kg-1 was consistent with the protocol specified dose.

Vecuronium group
Five subjects discontinued prior to treatment with IP and 1 subject was erroneously treated with rocuronium + neostigmine. This resulted in a total of 46 subjects who were treated with vecuronium and sugammadex and completed the trial. Thirty six patients were treated with vecuronium and neostigmine; 35 treated subjects completed the trial. All subjects received an intubating dose of vecuronium. A maintenance dose of vecuronium was not administered to 4 subjects in the sugammadex group and 4 subjects in the neostigmine group. For the subjects who received maintenance doses of vecuronium, the median dose of 0.01 mg.kg-1

Baseline data
Rocuronium group
The treatment groups were generally comparable with respect to demographics and other baseline characteristics. Overall, mean (median) age for subjects treated with rocuronium was 53 (54) years, ranging from 19-85 years; 56% of the subjects were female. The majority of subjects was White/Caucasian (88%) and of ASA Class 2 (73%).

Vecuronium group

Overall, mean (median) age for subjects treated with vecuronium was 53 (56) years, ranging from 25 to 78 years; 54% of the subjects were female. The majority of subjects was White/Caucasian (85%) and of ASA Class 2 (68%).

The treatment groups differed for some of the demographic characteristics. In comparison with the neostigmine group, the sugammadex group showed a younger mean age (50 vs. 57 years), and a higher percentage of females (63% vs. 42%) and Blacks (13% vs. 3%). Overall, the sugammadex group had a higher proportion of healthier subjects, with a lower percentage of ASA Class 3 subjects and a higher percentage of ASA Class 1 and 2 subjects. It is unlikely that the small differences on the demographic parameters may affect the interpretations of the results**.**

Numbers analysed

Rocuronium group

The ITT Group was based on the number of subjects who received IP and had at least one post-baseline efficacy assessment, according to their randomized treatment group. This resulted in a total of 74 subjects in the ITT Group, including 37 subjects in the rocuronium + sugammadex group and 37 subjects in the rocuronium + neostigmine group. Of the 74 subjects in the ITT Group, 11 had a major protocol violation resulting in a total of 63 subjects in the PP Group: 32 subjects in the rocuronium + sugammadex group and 31 subjects in the rocuronium + neostigmine group.

Vecuronium group

The ITT Group was based on the number of subjects who received IP and had at least one post-baseline efficacy assessment, according to their randomized treatment group. This resulted in a total of 83 subjects in the ITT Group, including 47 subjects in the vecuronium + sugammadex group and 36 subjects in the vecuronium + neostigmine group. Of the 83 subjects in the ITT Group, 15 had a major protocol violation resulting in a total of 68 subjects in the PP Group: 38 subjects in the vecuronium + sugammadex group and 30 subjects in the vecuronium + neostigmine group.

Outcomes and estimation

It is unusual in clinical practise to relax a patient that they would have this deep NMB (1-2 PTC). Thus the reversal of NMB of this level is not routine. In this study, the number of ASA 3 patient was low.

Rocuronium group

Table Summary of the time (min) from start of administration of sugammadex or neostigmine **administered at 1-2 PTCs** following rocuronium to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

	Trial 19.4.302	
	Rocuronium + **sugammadex** (4.0 $mg.kg^{-1}$)	**Rocuronium** + **Neostigmine** (70 $\mu g.kg^{-1}$)
n	37	37
Geometric Mean	2.9	50.4
95% CI	2.5 – 3.4	43.5 – 58.4
Median	2.7	49.0
Min. – max.	1.2 – 16.1	13.3 – 145.7
p-value[a]	<0.001	

[a] P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.

It was estimated that the time, from administration of sugammadex to recovery of the T4/T1 ratio to 0.9, was 24.4 times faster compared to the time from administration of neostigmine to recovery of the T4/T1 ratio to 0.9. The lower limit of the corresponding 97.665% CI was 18.3.

Vecuronium group

Table Summary of the time (min) from start of administration of sugammadex or neostigmine **administered at 1-2 PTCs** following vecuronium to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

	Trial 19.4.302	
	Vecuronium + sugammadex (4.0 mg.kg-1)	**Vecuronium + Neostigmine** (70 $\mu g.kg^{-1}$)
n	47	36
Geometric Mean	4.5	66.2
95% CI	3.3 – 6.0	55.6 – 78.9
Median	3.3	49.9
Min. – max.	1.4 – 68.4	46.0 – 312.7
p-value[a]	<0.001	

[a] P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.

It was estimated that the time, from administration of sugammadex to recovery of the T4/T1 ratio to 0.9, was 20.9 times faster compared to the time from administration of neostigmine to recovery of the T4/T1 ratio to 0.9. The lower limit of the corresponding one-sided 97.665% CI was 12.3.

The time to recovery of the T4/T1 ratio to 0.9 was significantly faster with sugammadex than with neostigmine, when the reversal agent was administered after rocuronium- and vecuronium-induced NMB. However, it should be noted that there was a high interindividual variation on recovery of the T4/T1 ratio to 0.9 when sugammadex 4 mg.kg-1 was administered at 1-2 PTC.

Ancillary analyses

Table 11 **Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 for subjects who received an intubating dose only and those who received an intubating dose and at least one maintenance dose (ITT group)**

		Intubating dose only	Intubating dose and maintenance dose(s)
Including imputed data	n	18	16
	Geometric mean	2:10	1:53
	Mean (SD)	2:33 (1:34)	2:02 (0:58)
	Median	2:16	1:49
	Min. – max.	0:41 - 6:24	1:07 - 5:07
Complete cases	n	17	15
	Geometric mean	2:04	1:45
	Mean (SD)	2:24 (1:28)	1:50 (0:32)
	Median	2:11	1:43
	Min. – max.	0:41 - 6:24	1:07 - 3:05

Data were taken from Appendix F, Table 6.1-C

These times suggest that reversal of neuromuscular blockade by sugammadex is not affected by the last dose of rocuronium administered: intubating dose (0.6 mg.kg-1) and intubating dose and at least one maintenance dose (0.10 to 0.20 mg.kg-1).

Study supporting the proposed indication: immediate reversal of a rocuronium induced NMB

- **Trial 19.4.303** compared reversal of a NMB induced by 1.2 mg.kg^{-1} rocuronium with 16 mg.kg^{-1} sugammadex (administered at 3 minutes following rocuronium) versus spontaneous recovery from 1.0 mg.kg^{-1} succinylcholine.

Table 57 Overview of clinical efficacy trials

Protocol no.[1] No. of centers (country) Trial status (start–end dates)	Trial objectives	Trial design	Trial & control drugs Dosage form (product ID/batch) Dose, route, regimen, & duration	Diagnosis (inclusion criteria)	Enrolled/treated/ completed, by trial arm	Gender[a] M/F	Age (yr) [a] Mean/median/ range	Primary endpoint
19.4.303 11 centers (USA, Canada) Complete (February 2006 – August 2006)	To demonstrate faster recovery to T_1 10% and 90% after 1.2 mg/kg rocuronium reversed at 3 min by 16.0 mg/kg Org 25969 compared to recovery after 1.0 mg/kg succinylcholine. To evaluate the safety of both treatments.	Multi-center, randomized, parallel group, comparative, active controlled, safety-assessor blinded trial.	Org 25969: 100 mg/mL (CY039). Dose: 16.0 mg/kg iv single dose Rocuronium bromide: 10 mg/mL (1910804592). Dose: 1.2 mg/kg iv, single dose. Quelicin® (succinylcholine chloride Injection USP) 20 mg/mL (25-266-EV and 36-125-EV). Dose: 1.0 mg/kg iv single dose	Age 18 and 65 years of age, ASA Class 1 or 2, scheduled to undergo a surgical procedure in supine position under general anesthesia requiring a short duration of neuromuscular relaxation with the use of rocuronium or succinylcholine and requiring endotracheal intubation, BMI of <30	Rocuronium + Org 25969: 57/56/55 Succinylcholine: 58/54/53	Rocuronium + Org 25969: 23/33 Succinylcholine: 23/31	Rocuronium + Org 25969: 42/44/18-63 Succinylcholine : 41/43/19-65	Time from start administration of NMBA to recovery of T_1 to 10%

METHODS

Study Participants

See table above.

Treatments

Each subject was to be randomized to one of the two treatment groups: rocuronium + sugammadex or succinylcholine. Subjects in the rocuronium + sugammadex group were to receive an intubation dose of 1.2 mg.kg-1 rocuronium and the neuromuscular blockade was to be reversed at 3 min after the start of administration of rocuronium with 16.0 mg.kg-1 sugammadex. Subjects in the succinylcholine group were to receive an intubation dose of 1.0 mg.kg-1 succinylcholine and allowed to recover spontaneously from the neuromuscular blockade.

Objectives

The **primary** objective was to demonstrate faster recovery to T1 10% after neuromuscular blockade induced by 1.2 mg.kg-1 rocuronium reversed at 3 minutes by 16.0 mg.kg-1 sugammadex compared to recovery after a neuromuscular blockade induced by 1.0 mg.kg-1 succinylcholine.

The **secondary** objectives were:

- To demonstrate faster recovery to T1 90% after neuromuscular blockade induced by 1.2 mg.kg-1 rocuronium reversed at 3 minutes by 16.0 mg.kg-1 sugammadex compared to recovery after a neuromuscular blockade induced by 1.0 mg.kg-1 succinylcholine.
- To evaluate the safety of a single dose of 1.2 mg.kg-1 rocuronium reversed at 3 minutes by 16.0 mg.kg-1 sugammadex and 1.0 mg.kg-1 succinylcholine in adult subjects.

Outcomes/endpoints

The primary efficacy variable was the recovery of T1 to 10% from start of rocuronium or succinylcholine administration.

The secondary efficacy variable was the recovery of T1 to 90% from start of rocuronium or succinylcholine administration.

Efficacy was based on evaluation of neuromuscular functioning as measured by acceleromyography (TOF-Watch and clinical signs of recovery).

Sample size

The time to T1 10% after a dose of 1.0 mg.kg-1 succinylcholine was measured in a study reported by Kopman et al. The mean (SD) time to T1 10% was 6.2 (0.8) min (n=16).

For the primary efficacy parameter in this trial, no data were available for sugammadex. However, for the sample size calculations, a standard deviation was assumed between 0.8 and 1.5 min. A difference between two treatments in time to T1 10% of more than 1 min was to be detected with a probability of 90% (power = 90%). Simulations indicated that a sample size of 49 per treatment group was sufficient. Taking into account that about 5% of the subjects would drop out from the ITT evaluation, the sample size was to be 52 per group. In order to evenly distribute the enrolment to 11 sites, the sample size was 55 per group (5 subjects per treatment group per site).

Randomisation
The subject allocation numbers were to be assigned to subjects in sequential order of their enrolment in the trial. At each trial centre, the first subject enrolled received the first site subject allocation number (the lowest) and the assigned treatment group in the Randomization Schedule.

Blinding (masking)
The person who prepared the medication was not to perform any subjective safety assessments for any of the subjects, and the safety assessor was not allowed to witness the preparation of the IP.

Statistical methods
Demographic, baseline, exposure and safety data were summarized by treatment group. Times from start of administration of rocuronium or succinylcholine to recovery of T1 to 10% and recovery of T1 to 90% were compared using a two-way analysis of variance (ANOVA) model. P-values and estimates for the treatment difference between the two treatment groups with corresponding two-sided 95% confidence interval, are presented. For the ITT population two evaluations were performed: one for which missing recovery times were imputed and one that used only the available recovery times. Clinical signs of recovery were summarized by treatment group only.

RESULTS
Participant flow
The following table presents the number of subjects in each subject data set, within and across treatment group.

Table Number of subjects in each subject data set, within and across treatment group

Subject data set	Treatment group		
	Rocuronium + Org 25969 (n)	Succinylcholine (n)	Total (n)
All-Subjects-Randomized	57	58	115
All-Subjects-Treated [a)]	56	54	110
Intent-to-Treat [b)]	55	55	110
Per-Protocol	32	41	73

Data were taken from Appendix F, Table 1.5-A.
a) The All-Subjects-Treated Group was based on actual treatment received. One subject randomized to the rocuronium + Org 25969 group was treated with succinylcholine, and 2 subjects randomized to the succinylcholine group were treated with rocuronium and Org 25969.
b) The Intent-to-Treat Group was based on the randomized treatment group.

Recruitment
A total of 115 subjects were randomized to a treatment group, including 57 subjects in the rocuronium + sugammadex group and 58 subjects in the succinylcholine group.

Conduct of the study
A total of 7 subjects discontinued prematurely from the trial, including 5 non-treated subjects and 2 treated subjects. According to randomized treatment group, 55 subjects in the rocuronium + sugammadex group and 55 subjects in the succinylcholine group were treated with trial medication. However, 3 subjects received trial medication that was not consistent with their randomized treatment group: 1 subject in the rocuronium + sugammadex group was treated with succinylcholine, and 2

subjects in the succinylcholine group were treated with rocuronium and sugammadex. With the exception of 1 subject in the rocuronium + sugammadex group, all subjects in the All-Subjects-Treated Group received a dose of rocuronium, sugammadex, or succinylcholine within 10% of the protocol-defined dose. One patient received 1.6 mg.kg-1 sugammadex, instead of 16.0 mg.kg-1.

Baseline data
Overall, mean (median) age was 42 (43) years, ranging from 18-65 years; 58% of the subjects were female and 42% were male. The majority of subjects in both treatment groups was White/Caucasian, although the percentage of Black (or African American) was higher in the rocuronium + sugammadex group (20%) in comparison with the succinylcholine group (9%). Most of the subjects were classified ASA Class 2 (59%, rocuronium + sugammadex group; 69%, succinylcholine group). Mean (SD) BMI was 25 (3) kg/m2 in both treatment groups.

Numbers analysed
The ITT Group was based on the number of randomized subjects who had at least one post-baseline efficacy assessment. While all treated subjects had at least one post-baseline efficacy assessment, the three subjects who received the wrong trial medication were included under the treatment group to which they were randomized. This resulted in a total of 110 subjects in the ITT Group, including 55 subjects in the rocuronium + sugammadex group and 55 subjects in the succinylcholine group. Of the 110 subjects in the ITT Group, 37 had a major protocol violation resulting in a total of 73 subjects in the PP Group: 32 subjects in the rocuronium + sugammadex group and 41 subjects in the succinylcholine group.

Outcomes and estimation

Table Summary of the time (min) from start of administration of sugammadex or succinylcholine to **recovery of T1 to 10% and to 90%** (ITT group)

	Trial 19.4.303	
	Rocuronium + **sugammadex** (16.0 mg.kg^{-1})	**Succinylcholine** (1.0 mg.kg^{-1})
Time to T_1 of 10%		
n	55	55
Mean (SD)	4.4 (0.7)	7.1 (1.6)
Median	4.2	7.1
Min. – max.	3.5 – 7.7	3.7 – 10.5
p-value[a]	<0.001	
Time to T_1 of 90%		
n	55	55
Mean (SD)	6.2 (1.83)	10.9 (2.42)
Median	5.7	10.7
Min. – max.	4.2 – 13.6	5.0 – 16.2
p-value[a]	<0.001	

[a] P-value obtained from a 2-way ANOVA on the time to T_1 10% / 90%.

It was estimated that the mean time from administration of rocuronium to recovery of T1 to 10% was statistically significantly faster (185 sec [3min: 5 sec]) compared with the mean time from administration of succinylcholine to recovery of T1 to 10%. The 95% CI ranged from -218 to -153 sec (-3 min:38 sec to -2 min:33 sec).

The result of the secondary efficacy variable is in line with the primary, showing a clear treatment difference. Relative to the time of administration of Org 25969, the recovery times of T_4/T_1 ratios to 0.7, 0.8 and 0.9 were 1.3, 1.5, and 2.2 minutes, respectively.
Ancillary analyses

In an ancillary analysis the recovery of the T4/T1 ratio to 0.9 was analysed, and it was noticed that most patients had recovery by 3 min (87%), see following table.

Table Summary of times (min:sec) from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9, by treatment group (ITT Group)

		Rocuronium + sugammadex (N=55)	Succinylcholine (N=55)
Time from start of administration of sugammadex to recovery T4/T1 ratio to 0.9 (min:sec)	n Mean (SD) Median Min. - max.	54 2:14 (2:12) 1:44 0:29 - 14:18	NA

Sugammadex 16.0 mg.kg^{-1} administered 3 minutes after rocuronium 1.2 mg.kg^{-1} provided rather rapid recovery of the T4/T1 ratio to 0.9, which is considered a clinically relevant end-point and should be sufficient for most patients in critical incidences where immediate reversal of NMB is necessary.

- Analysis performed across trials (pooled analyses and meta-analysis)

Routine reversal - Reversal at reappearance of T2
Administration of a dose of 2.0 mg.kg-1 sugammadex at reappearance of T2 after rocuronium or vecuronium during intravenous (propofol) or inhalational anaesthesia (sevoflurane) in 477 patients in 13 Clinical Trials in a mean recovery of the T4/T1 ratio to 0.9 well within 3 minutes. This is much faster than spontaneous recovery (39.9 minutes) or recovery after currently available reversal agents like neostigmine (18.5 minutes).

Routine reversal - Reversal at 1-2 PTC
Administration of a dose of 4.0 mg.kg-1 sugammadex at 1-2 PTC in 129 patients in four Clinical Trials resulted in a mean recovery of the T4/T1 ratio to 0.9 within 3 minutes after rocuronium and within 5 minutes after vecuronium. Administering maintenance doses of vecuronium instead of only an intubating dose delayed recovery time.

Immediate reversal - Reversal 3 minutes after rocuronium
Administration of a dose of 16.0 mg.kg-1 sugammadex 3 minutes after a dose of 1.2 mg.kg-1 rocuronium in 65 patients in two Clinical Trials resulted in a mean recovery of the T4/T1 ratio to 0.9 of 1.7 minutes.

Pooled data indicates that the recovery by 4.0 mg.kg-1 sugammadex after maintenance doses of vecuronium takes longer than after an intubating dose alone.

- Clinical studies in special populations

Five trials were conducted in special subject populations where Bridion was administered at a shallow block induced by Rocuronium. Reversal of vecuronium has not been investigated in special populations.

These five trials included:
1. Trial 19.4.304 performed in subjects with renal failure.
2. Trial 19.4.305 performed in elderly subjects.
3. Trial 19.4.306 performed in paediatric subjects
4. Trial 19.4.308 performed in subjects with pulmonary complications.
5. Trial 19.4.309 performed in subjects with cardiac complications

The efficacy results are given below:

1. Trial 19.4.304 in subjects with renal failure

This study was conducted to compare the efficacy of sugammadex and the PK profile of 2.0 mg.kg^{-1} sugammadex (and rocuronium) when administered at the reappearance of T_2 following rocuronium-induced NMB in subjects with renal disease and healthy controls. Subjects under investigation were ASA class 1 - 3 for renally impaired patients and ASA class 1-2 for control group.

A total of 30 subjects, 15 with CR_{CL} <30 ml/min (renal impaired group) and 15 with CR_{CL} ≥80 ml/min (normal control group), each received a single, bolus intravenous dose of 0.6 mg/kg rocuronium, followed by a single, bolus, intravenous dose of 2 mg/kg Bridion at reappearance of T_2.

The mean time from start of administration of Bridion to recovery of the T_4/T_1 ratio to 0.9 was 2.0 minutes for the renally impaired subjects and 1 min:39 sec for the control subjects.

Based on the prespecified full ANOVA model, the estimated mean absolute difference between the renally impaired and control subjects were +27.3 seconds. The corresponding 95% CI ranged from -10.9 to +65.5 seconds. The CI was not completely within the pre-defined equivalence interval of-60 to +60 seconds and equivalence could not be claimed between the two groups.

Based on the additive ANOVA model, the estimated mean absolute difference was +20.1 seconds and the corresponding 95% CI ranged from -12.1 to +52.3 seconds. This CI was within the pre-defined equivalence interval.

This small study indicates that there may not be differences in the recovery of rocuronium-induced NMB when sugammadex 2.0 mg.kg^{-1} is administered at the reappearance of T_2 between subjects with renal disease and the healthy controls.

2. Trial 19.4.305 in elderly subjects

This study was a multicenter, parallel group, comparative trial to compare the efficacy of sugammadex in elderly subjects with adult subjects.

A total of 48 subjects aged 18-64 years, and 62 subjects aged 65-74 years, and 40 subjects aged ≥75 years, received a single bolus intravenous dose of 2.0 mg/kg Org after the last dose of rocuronium and at the reappearance of T_2.

The geometric mean time from administration of Bridion to recovery of the T_4/T_1 ratio to 0.9 was 2 min:16 sec in the adult group and 2 min:56 sec in the geriatric group, when missing data were imputed.

The time from administration of Bridion to recovery of the T_4/T_1 ratio to 0.9 was estimated to be 0.70 min slower for the geriatric group than for the adult group. Data indicated that the time from administration of Bridion to recovery of the T_4/T_1 ratio to 0.9 for the 65-74 age group was about 20 seconds (on average) slower than for the 18-64 age group. For the 75+ age group the time was more than one minute (on average) slower than for the 18-64 age group.

Exploratory analysis indicated that reversal of neuromuscular block by Bridion did not differ between subjects who received only an intubating dose of rocuronium compared to subjects who received at least one maintenance dose as well.

3. Trial 19.4.306 in paediatric subjects

This was a phase III, multi-centre, randomized, parallel dose-finding, placebo controlled, and safety assessor blinded trial to explore the efficacy, safety and pharmacokinetics of Bridion in paediatric and adult subjects.

Subjects of ASA class 1-2, between the ages of 28 days and 65 years, scheduled for general anaesthesia with anticipated duration of anaesthesia of at least 60 minutes, without further need for muscle relaxation other than one single dose of 0.6 mg/kg rocuronium were included in the trial.

One-hundred twenty subjects were enrolled, six per dose group and per age group. The dose groups were 0.5, 1.0, 2.0, or 4.0 mg/kg Bridion or placebo. The age groups were: Infants (28 days - 23 month), children (2-11 years), adolescents (12 – 17 years) and adults (18 -65 years). A total of 91 subjects (8 infants, 24 children, 31 adolescents, and 28 adults) received a single, bolus, intravenous dose of Bridion (0.5, 1, 2, or 4 mg/kg) or placebo. A total of 90 subjects completed the trial.

Primary efficacy variable was time from start of administration of sugammadex to recovery of T_4/T_1 ratio to 0.9.

The results are presented in the table below.

Table Org 25969 administered at reappearance of T_2 following rocuronium administration: summary of the time to recovery of T_4/T_1 to 0.9 (min) by age group and dose, Clinical Trial 19.4.306 (PP group)

	Dose group				
	Placebo	0.5 mg/kg Org 25969	1.0 mg/kg Org 25969	2.0 mg/kg Org 25969	4.0 mg/kg Org 25969
Infants n	2	2	2	1	1
Mean (SD)	21.0 (11.3)	3.7 (0.6)	2.4 (0.7)	0.6 (-)	0.7 (-)
Median	21.0	3.7	2.4	0.6	0.7
Min. – max.	13.0 – 29.0	3.3 – 4.2	1.9 – 2.9	0.6 – 0.6	0.7 – 0.7
Children n	4	5	5	4	4
Mean (SD)	19.6 (11.0)	5.2 (3.5)	4.0 (3.2)	1.2 (0.4)	1.6 (1.9)
Median	19.0	3.7	2.7	1.2	0.6
Min. – max.	8.4 – 31.8	2.4 – 10.9	1.9 – 9.6	0.9 – 1.6	0.6 – 4.4
Adolescents n	5	5	6	6	6
Mean (SD)	22.8 (13.1)	12.0 (17.7)	1.8 (0.4)	1.9 (1.7)	1.1 (0.2)
Median	23.4	4.6	1.7	1.1	1.1
Min. – max.	6.8 – 41.7	1.9 – 43.5	1.5 – 2.5	0.7 – 5.2	0.7 – 1.4
Adults n	6	5	5	5	5
Mean (SD)	29.5 (8.4)	3.8 (1.1)	1.6 (0.3)	1.3 (0.3)	1.4 (0.4)
Median	28.5	4.2	1.7	1.2	1.4
Min. – max.	19.6 – 44.0	2.3 – 4.8	1.2 – 2.0	0.9 – 1.6	1.0 – 2.0

It was concluded that for children, adolescents and adults a clear dose-response relationship was found. On the contrary, in infants, the mean time to recovery of the T4/T1 ratio to 0.9 markedly decreased with increasing dose of sugammadex. However no plateau, i.e. no limit of recovery was reached and no dose-response effect could be demonstrated. This was due to the low number of infants (one or two infants in each of the dose groups). Plasma concentrations of sugammadex were approximately dose proportional over the dose range of 0.5 to 4.0 mg.kg-1 in all age groups. No recurarization was observed.

The safety data indicate that sugammadex was well tolerated by the paediatric and adult subjects. The results of infants should be interpreted with care due to the low number of infants in the trial. Of the two SAEs that occurred in this trial, one occurred in an infant and the other in a child.

4. Trial 19.4.308 in subjects at increased risk of pulmonary complications

This was a multi-centre, randomized, parallel group, comparative, safety-assessor blinded trial in adult surgical subjects under general anaesthesia at increased risk for pulmonary complications (i.e. subjects with a history of or a diagnosis of pulmonary disease).

A total of 77 subjects were treated and completed the trial: 39 subjects received 2.0 mg/kg Bridion and 38 subjects received 4.0 mg/kg Bridion as single bolus intravenous doses at the reappearance of T_2 following the last dose of rocuronium.

The objectives were to evaluate the safety and efficacy of 2.0 and 4.0 mg.kg-1 sugammadex after a neuromuscular block induced by rocuronium after reversal at reappearance of T2.

The geometric mean time from administration of 2.0 mg.kg-1 sugammadex and 4.0 mg.kg-1 sugammadex to recovery of the T4/T1 ratio to 0.9 were 2.1 min and 1.8 min, respectively. The time from the start of the administration of IP to recovery of the T4/T1 ratio to 0.9 ranged from 0.8 min to 12.0 min in the 2.0 mg.kg-1 sugammadex group, and from 0.7 min to 11.5 min in the 4.0 mg.kg-1 sugammadex group. For two subjects a long recovery time was observed (12.0 minutes for one subject in the 2.0 mg.kg-1 group and 11.5 minutes for one subject in the 4.0 mg.kg-1 group).

5. Trial 19.4.309 Subjects with cardiac complications

This was a multi-centre, randomized, parallel-group, placebo-controlled, safety-assessor blinded trial, evaluating the safety and efficacy of sugammadex in cardiac patients.

Cardiopathic patients were those with ischemic heart disease, chronic heart failure or arrhythmia), of NYHA Class II to III, they were ASA class maximally 4 (class 4 only because of NYHA class III), aged at least 18 years, scheduled for elective, noncardiac surgery under general anaesthesia with propofol in the supine position, with planned muscle relaxation using rocuronium.

In total 121 subjects were randomized and 116 subjects were treated: 38 subjects with 2.0 mg.kg-1 sugammadex, 38 subjects with 4.0 mg.kg-1 sugammadex and 40 with placebo. In total 116 subjects completed the trial. The trial medications were administered as single bolus intravenous doses at the reappearance of T_2 following the last dose of rocuronium.

The trial indicates that sugammadex at dose levels of 2.0 and 4.0 mg.kg-1 is effective in cardiac patients; the mean times from the start of the administration of sugammadex to recovery of the T4/T1 ratio to 0.9 were 36.9 min in the placebo group and 1.7 min and 1.4 min respectively in the 2.0 and 4.0 mg.kg-1 sugammadex dose groups. Furthermore the 4.0 mg.kg-1 sugammadex group had a faster mean recovery than the 2.0 mg.kg-1 sugammadex group according to the point estimates (difference in geometric means of 23 seconds).

- Supportive studies

Trial 19.4.210, investigating the use of Bridion in subjects receiving propofol anaesthesia or sevoflurane anesthesia.

This was a multi-center, randomized, safety assessor-blinded, phase II parallel group comparative trial in subjects of ASA class I-III comparing efficacy and safety of Bridion administered in subjects receiving anesthesia using propofol compared to subjects receiving anaesthesia using sevoflurane.

The primary objective was to show equivalence in recovery to T_4/T_1 ratio of 0.9 after reversal with Bridion at reappearance of T_2 between subjects receiving anesthesia using propofol or sevoflurane.

All subjects received rocuronium 0.6 mg/kg as neuromuscular blocking agent, followed by 2.0 mg/kg of Bridion at reappearance of T_2. Anaesthesia was maintained using either propofol > 6.0 mg/kg/h or sevoflurane, target minimal alveolar concentration 1.5 (adjusted for age), in random order and according to clinical need and at least until recovery of the T_4/T_1 ratio to 0.9.

A total of 42 subjects was randomized, treated and completed the trial (21 subjects per group).

The mean time from start of administration of Bridion to recovery of the T_4/T_1 ratio to 0.9 was 1 min:48 sec for subjects who received maintenance of anesthesia with sevoflurane, and 1 min:50 sec for subjects with maintenance of anesthesia using propofol.

The estimated mean difference was -1 second, with the corresponding 95% CI ranging from -28 to +26 seconds.

Trial 19.4.311

According to the applicant this trial was conducted to determine the safety and time-course of recovery to a T_4/T_1 ratio of 0.9 within 4 minutes after 4.0 mg/kg Bridion given at least 15 minutes after the last administration of rocuronium in a wide range of surgical procedures and anaesthetic regimens.

This trial was designed to mimic the use of sugammadex in normal daily practice in different anaesthetic regimens and a wide range of anaesthetic procedures. Each subject was to receive an intravenous single bolus dose of 0.6 $mg.kg^{-1}$ rocuronium for endotracheal intubation. If further NMB was required, maintenance doses of 0.15 $mg.kg^{-1}$ rocuronium could be administered. The NMB was to be reversed, at least 15 minutes after the last dose of rocuronium, with a dose of 4.0 $mg.kg^{-1}$ sugammadex. One hundred and thirty four (134) patients received at least one maintenance dose of rocuronium.

The median value of the mean maintenance dose was 0.15 mg.kg-1 and the median number of maintenance doses administered to the subjects was 3. The individual number of maintenance doses ranged from 1 to 16.158 (89%) out of 177 subjects recovered to a T_4/T_1 of 0.9 within 4 minutes of receiving 4.0 $mg.kg^{-1}$ sugammadex. The mean time from administration of sugammadex after an intubating dose of rocuronium to recovery of the T_4/T_1 ratio to 0.9 was 2.0 minutes compared to 1.9 minutes in subjects who received an intubating dose and at least one maintenance dose of rocuronium.

- Discussion on clinical efficacy

The Applicant has demonstrated that sugammadex, which is selective for steroidal neuromuscular blocking agents, can rapidly encapsulate free steroidal NMBAs, e.g. rocuronium and vecuronium, thereby preventing their pharmacological actions in the neuromuscular junction in a dose dependant manner. However, sugammadex does not reverse neuromuscular block induced by succinylcholine or benzylisoquinolium compounds, and thus anticholinesterases are needed for reversal of benzylisoquinolone-induced NMB.

With respect to the model development and the Applicant has updated and redeveloped parts of the PKPD interaction model. However, it is advised that the full PKPD interaction model should be updated for future predictions; the aim being to develop one model that includes predictions for as many sub-populations as possible. The applicant has committed to present a plan for the update of the model as stated in their letter of undertaking dated 28 May 2008.

In the PK studies, the changes in the APTT, PT (inr) and PT in the presence of Bridion and Org 48302 in in vitro tests suggest interference of these drugs with coagulation cascade. As a follow-up, in study 19.4.115, the applicant has committed to investigate the effects of Bridion on coagulation in volunteers and the applicant has agreed to provide this information as a post-authorisation commitment, as stated in their letter of undertaking dated 28 May 2008. There will also be an in vitro part, in which several coagulation tests with different Bridion concentrations will be tested.

The clinical data submitted from 29 clinical trials, including 14 Phase II and 10 Phase III clinical trials, has been considered sufficient to provide evidence to support the use of Bridion in the three clinical settings i.e. reversal of shallow (moderate) or profound (deep) block, and also in the immediate reversal of NMB, in the airway emergency situation.

In two of the Phase III trials (Trial **19.4.301** & Trial **19.4.310**) that specifically investigated the reversal of a shallow (moderate) block **(routine reversal at the reappearance of T_2)**, administration of Bridion resulted in a more rapid recovery from NMB when compared to neostigmine as reversal agent. This was true for the reversal of NMB induced by both rocuronium and vecuronium. Routine reversal of shallow block resulted in a slightly faster recovery time in the rocuronium group as compared to the vecuronium. The geometric mean time to recovery from a shallow block was 1.5 minutes in the rocuronium group and 2.8 minutes in the vecuronium group. Furthermore, reversal of neuromuscular blockade by Bridion appears not to be affected by the last dose of rocuronium but was slightly prolonged in subjects received maintenance doses of vecuronium.

Although, the currently reversal strategy involves the convenience of using the same antagonist (neostigmine) to reverse of all non-depolarising NMBA and the fact that Bridion does not antagonize

residual block induced by benzylisoquinolinium relaxants such as atracurium, mivacurium and cis-atracurium, the introduction of a new reversal agent - specifically for the reversal of rocuronium and vecuronium, resulting in a faster recovery of NMB may also have an impact on the choice of NMBA to be used in the routine clinical setting. The use of sugammadex in common anaesthesia practice has been reflected in section 4.2 of the SPC, posology.

In the pivotal trial (Trial **19.4.302)** investigating reversal from a profound (deep) NMB (**routine reversal at 1-2 PTCs**), a large difference in mean recovery time was seen when Bridion was compared with neostigmine. The geometric mean time to recovery from a profound block was 2.9 minutes in the rocuronium group and 4.5 minutes in the vecuronium group. The efficacy results in both the rocuronium and vecuronium groups confirm that Bridion can be used in reversal of a profound NMB. The requirement to obtain some degree of spontaneous recovery will no longer be present.

The mean difference in recovery time of 47 minutes in the rocuronium group, and 61 minutes in the vecuronium group when compared to neostigmine group probably mirrors the known fact that the currently available reversal agents such as neostigmine is not nearly as effective as a reversal agent at a profound block.

The Applicant has clarified that doubling of the dose from 4 to 8 mg/kg Bridion in the situation where reversal would take place at 1-2 PTC resulted in a reduction of the median time of recovery to a TOF 0.9 from 1.6 minutes to 1.2 minutes in rocuronium patients and a reduction from 2.1 minutes to 1.5 minutes in vecuronium patients. A further reduction of less than a minute was not considered to be clinically significant.

In most surgical procedures a profound block is not needed but in the surgical procedure where a profound block is required the use of Bridion and subsequently the rapid recovery of the neuromuscular function would be of clinical value. Of the non-depolarizing neuromuscular blocking drugs available, rocuronium has the most rapid onset of action. In situations where a return to spontaneous ventilation is desirable, rocuronium followed by Bridion may be considered as good choice.

In the clinical trial (Trial **19.4.303)** investigating the "**Immediate reversal**" setting, a statistically significant treatment difference was observed in the recovery time between the different treatment groups. The mean recovery time from administration of the NMBA of 4 min:22 sec in the rocuronium + Bridion group compared to 7 min:4 sec in the succinylcholine group is considered as highly clinically relevant in the emergency airway setting in which currently no reversal agent is available.

It must be emphasized though, that the administration of Bridion is not the one and only solution for the emergency situation of a cannot-intubate-cannot-ventilate (CICV) scenario. The administration of Bridion will only partially solve the situation of CICV as the patient is not only receiving muscle relaxant but also anaesthetics and opioids, which also unable spontaneous breathing. Moreover, if the patient can not be intubated nor ventilated in 4 min:22 sec from the administration of NMBA (time of administration of Bridion to the recovery times of T_4/T_1 0.9 was 2.2 minutes) this is considered too long a time to solely await recovery of spontaneous breathing, and the handling of the patients almost always adhere to "the flowchart for the difficult airway" including the usage of different technical measures to facilitate intubation and finally the consideration of an acute tracheotomy, even though Bridion has been administered. However it should be pointed out that Bridion will provide the physician with a most valuable tool in a CICV scenario if the NMB was induced by rocuronium. There is an unmet clinical need for a drug that can reverse a profound block induced by NMBA in a **cannot-intubate-cannot-ventilate (CICV)** situation.

No trials were conducted to investigate the efficacy of sugammadex in immediate reversal situations following a pancuronium- and vecuronium-induced NMB.

It is also noted that the efficacy and safety of the proposed dose has been evaluated only in ASA I–III adult patients who were reasonably healthy.

In conclusion, statistically significant and clinically relevant effects in favour of Bridion have been found in the primary analysis (ITT with imputed data) of all pivotal studies. The findings were considered to be robust and consistent results were obtained in the ITT-complete cases and PP analyses as well as in the analyses of secondary efficacy variables.

Bridion results in a clinically significant reduction in recovery time as compared to established regimens in the reversal of a shallow (moderate; routine reversal at the reappearance of T_2) and profound (deep; routine reversal at 1-2 PTCs) NMB in routine clinical setting, and the requirement to obtain some degree of spontaneous recovery before a reversal agent can be administered, will no longer be present. In particular Bridion will provide the physician with a valuable tool of immediate reversal, in a CICV scenario if the NMB was induced by rocuronium.

Although no clinical trials were performed on the readministration of rocuronium and vecuronium, the Applicant has agreed that there should be a waiting time of 24 hours. In order to avoid the risk of confusion, one time-point for both rocuronium and vecuronium has been applied to all patients - irrespective of renal function or previously used dose of sugammadex. Therefore the overall recommended waiting times for reuse of rocuronium and vecuronium of 24 hours for all situations has been implemented in the SPC.

In addition, five trials were conducted in special subject populations e.g. in subjects with pulmonary or cardiac complications, in subjects with renal failure, in paediatric and in elderly subjects. With some minor differences, the efficacy results in special populations were comparable with the efficacy shown in healthy adult subjects when Bridion was administered at a shallow NMB induced by rocuronium. The recovery time was slightly prolonged in elderly subject >75 years (on average 1 minutes) and markedly decreased in paediatric subjects. The applicant has committed to investigate the safety of Bridion in severe renal impaired patients as stated in their letter of undertaking dated 28 May 2008.

Clinical safety

- Patient exposure

The safety data presented come from 29 completed clinical trials in which 1833 subjects were exposed to Bridion.

The **pooled Phase 1 dataset** includes a total of 120 subjects who received one or more doses of Bridion (representing 272 total exposures) and no NMBA, and 114 subjects who received a single dose of placebo and no NMBA.

The **pooled Phase 1-3 dataset** includes 1713 subjects (26 Phase 1 subjects and 1687 Phase 2-3 subjects) who received a single dose of Bridion and an NMBA, and 140 subjects (10 Phase 1 subjects and 130 Phase 2-3 subjects) who received a single dose of placebo and NMBA.

Most of the patients were between ages of 18-64 years, majority were Caucasian or Asian, only some Hispanic/Latino or Black people were studied. Safety data of Bridion in races other than Caucasian or Asian does not indicate any inconsistency with the profile seen in the general population with regard to adverse events, laboratory results, and vital signs.

Safety data on ASA 4 patients is very limited (1 subject). Additional ASA 4 patients will be included in future Phase IIIB studies.

Safety data on infants is limited and there is currently no data on neonates. At present, the use of Bridion in term newborn infants and infants is not recommended. Further paediatric studies are planned.

Safety data on patients over 75 years of age does not indicate any inconsistency with the profile seen in the general population with regard to adverse events, laboratory results, and vital signs.

Safety data on patients with haemodialysis or peritoneal dialysis is limited and the use of Bridion in severe renal impaired patients is currently not recommended. Further clinical trials are planned

- Adverse events

Two datasets were generated for the integrated analysis of safety:

1. Pooled Phase I Dataset

In this data set, adverse events were pooled for the 4 randomized, double blind Phase I crossover trials in which subjects received single doses of study medication but no anaesthetic or NMBA.

According to the applicant all AEs in the integrated database are coded to MedDRA version 9.1. Therefore, there are some differences between the coding in the integrated database compared to some individual trial reports that were originally coded to WHO-ART.

2. Pooled Phase I-III Data set

In this data set safety data were pooled from all trials in which Bridion or placebo were administrated following an NMBA (N=24). The dataset is referred to as **Total Bridion group** and includes data from **1713** subjects. Particular interest has focused on the doses of 2.0 mg/kg, 4.0 mg/kg and 16 mg/kg Bridion.

Within this dataset, two additional subsets were generated:

➢ *Dataset Bridion vs. Neostigmine:*

In this dataset safety data were pooled from the 2 Phase III trials in which Bridion was compared to neostigmine. Trials 19.4.301 and Trial 19.4.302 in which 179 subjects received Bridion and 167 subjects received neostigmine.

The incidence of subjects with at least one AE was similar for Bridion subjects (88%) and neostigmine subjects (89%). The overall incidence of AEs was similar between the two groups regardless of the NMBA administered, although it was slightly higher overall in the rocuronium group:

- Rocuronium plus Bridion (91%), rocuronium plus neostigmine (93%);
- Vecuronium plus Bridion (85%), vecuronium plus neostigmine (85%).

The AEs, those that occurred in at least 2% Bridion subjects and at least twice as frequently as in neostigmine subjects included flatulence and postoperative gastrointestinal disorder. Conversely, AEs in neostigmine subjects that occurred at least twice as frequently as in Bridion subjects included dizziness, procedural complication, dry mouth, oral pain, anxiety, procedural hypotension, anaemia, post procedural vomiting, dyspepsia, airway complication of anaesthesia, post procedural complication, erythema, and neuromuscular block prolonged.

➢ *Dataset Bridion vs. Placebo:*

In this dataset safety data were pooled from the 10 trials that included a placebo group in which 640 subjects received Bridion and 140 subjects received placebo.

Table Number of adult subjects exposed to Bridion or placebo in pooled Phase 1-3 trials with a placebo group by the type of NMBA

	Rocuronium +		Vecuronium +	
Trial phase	Org 25969	Placebo	Org 25969	Placebo
Phase 1	10	10	0	0
Phase 2	418	60	114	24
Phase 3	98	46	0	0
Total	526	116	114	24

Source: Appendix Table 5.
Notes: Pediatric subjects from trial 19.4.306 are excluded from this table.

The incidence of subjects with at least one AE was similar for Bridion subjects (68%) and placebo subjects (72%). The overall incidence of AEs was similar between the Bridion and placebo groups regardless of the NMBA administered, although it was higher overall in the vecuronium group:

- Rocuronium plus Bridion (67%), rocuronium plus placebo (70%)
- Vecuronium plus Bridion (75%), vecuronium plus placebo (83%)
- A total of 58% of the 19 subjects in the uncontrolled Bridion plus pancuronium group experienced at least one AE

The AEs that occurred in at least 2% Bridion subjects and at least twice as frequently as in placebo subjects included anaesthetic complication and cough. Adverse events in placebo subjects that occurred at least twice as frequently as in Bridion subjects included constipation, dysuria, paraesthesia, malaise, post procedural nausea, pruritus, anaemia, and ventricular extrasystoles.

The AE "anaesthetic complication" in either treatment group occurred only in subjects who received rocuronium (vs. vecuronium). Other complications of anaesthesia occurred infrequently and included the following:

- Airway complication of anaesthesia (1% Bridion, 0% placebo),
- Delayed recovery from anaesthesia (1% Bridion, 0% placebo),
- Unwanted awareness during anaesthesia (< 1% Bridion, 0% placebo), and
- Anaesthetic complication cardiac (< 1% Bridion, 0% placebo).

The group of "anaesthetic complications" observed with rocuronium or vecuronium were not reported in the small subset of 19 subjects who received pancuronium and Bridion. One subject in the pancuronium and Bridion group experienced prolonged neuromuscular block.

Phase 1 - 3 dose response studies
Overall, 80% of all subjects exposed to any dose of Bridion plus an NMBA (rocuronium, vecuronium, or pancuronium) experienced at least one AE. No dose response was apparent for the overall incidence of AEs.

The overall incidence of AEs was 79% in the 2 mg/kg group, 89% in the 4 ml/kg group, and 81% in the 16 mg/kg group.

Adverse events occurred in at least 2% of all Bridion subjects who received an NMBA in pooled Phase 1-3 trials. The most frequent (i.e., ≥ 20% incidence) adverse effects in the total Bridion group included injury, poisoning, and procedural complications (57% total Bridion), gastrointestinal disorders (38% total Bridion), and general disorders and administration site conditions (22% total Bridion). No dose response was apparent for AE incidence.

The most frequent (i.e., ≥ 5% incidence) AEs in the Bridion group included procedural pain, nausea, vomiting, pyrexia, headache, pharyngolaryngeal pain, constipation, dizziness, pain, and chills. AEs describing anaesthetic complications each occurred in 3% or less of the total Bridion group and included anaesthetic complication (3%), airway complication of anaesthesia (1%), prolonged neuromuscular block (< 1%), delayed recovery from anaesthesia (< 1%), unwanted awareness during anaesthesia (< 1%), and anaesthetic complication cardiac (< 1%).

Injection site irritation
In the Phase 1 studies one commonly occurring AE was injection site irritation. In some patients even paraesthesia enduring several days was reported. Erythema in the injection site has been also reported.

Electrocardiographic changes
In the Phase 1 study 194101 one male discontinued the study due to an adverse event; a Wolff-Parkinson-White-syndrome detected on the ECG recording 30 and 60 minutes after administration of 2.0 mg/kg Bridion. The subject had no symptoms at that moment and his vital signs were normal. The ECG was normal at 2 hours post-dose.

QTc changes
QT time in the ECG has been evaluated. In these evaluations QT has been corrected with heart rate using three methods Bazzet's and Fridericia's correction and correction with linear regression model. In Phase 1 studies prolongations of QTc in several healthy persons were noted.

There were significant prolongations in the QTc interval in all of the Phase 1-3 studies. Especially, the use of sevoflurane increased incidence of abnormally long QTc intervals. However, no *torsades des pointes* arrhythmia was noted in any of the study subjects.

The risk of a pharmacodynamic interaction on the QT interval can not be excluded for the combination of Bridion and Sevoflurane. In the phase II 19.4.210 study when Bridion was administered with sevoflurane or propofol a significant prolongation of QTc interval was recorded in a small patient population. Mean QTc interval prolongation in the sevoflurane group was in the range as reported in previous publications. Additionally, subjects in the propofol group had statistically significant QTcF prolongation. In the group of clinically important outliers, 11 out of the total 16 subjects had a concomitant medication which is known to prolong the QTc interval.

The QTc prolongation is a concern in clinical situations when many other drugs affecting QT-interval are used concomitantly. The data of Bridion and QTc prolongation is few and already in the 19.4.210 study population, clinically significant changes in QTc interval are noted. The applicant has committed to provide detailed evaluation of the QTc prolongations reported as SAEs in the clinical trials trials - particularly related to concomitant administered drugs (sevoflurane, propofol), as a post-authorisation commitment, as stated in their letter of undertaking dated 28 May 2008. The Applicant will also closely follow and report the QTc interval prolongations in PSURs.

Bridion vs. Placebo: Related AEs
More Bridion subjects (32%) than placebo subjects (7%) had related AEs. In both treatment groups, the overall incidence of related AEs in each system organ class (SOC) was < 20%.

The most frequent AE was Nervous System Disorders, and the incidence of related AEs in this class was higher in Bridion subjects (19%) than in placebo subjects (4%). Gastrointestinal system disorders also occurred more frequently in Bridion subjects (13%) than in placebo subjects (3%). Of the SOCs with a lower incidence of related AEs, at least twice as many Bridion subjects compared to placebo subjects had related AEs of the general disorders and administration site conditions SOC (5% Bridion, 2% placebo), the respiratory, thoracic, and mediastinal Disorders SOC (3% Bridion, 0% placebo), and the skin and subcutaneous tissue disorders SOC (3% Bridion, 1% placebo).

Related AEs that occurred in 2% or more of subjects in either treatment group were dysgeusia, nausea, headache, abdominal pain, dry mouth, dizziness, and salivary hypersecretion. Of these related AEs, all but headache occurred at least twice as frequently in Bridion subjects compared to placebo subjects.

Dysgeusia, nausea, abdominal pain and dizziness were also the AEs that occurred overall at least twice as frequently in Bridion subjects compared to placebo subjects and/or showed a dose trend. All occurrences of dysgeusia, nausea (reported only in Bridion subjects) and dizziness (reported only in Bridion subjects), were judged to be related to the trial medication by the investigator, abdominal pain were considered to be related by the investigator (in 6 of 9 Bridion subjects and in 1 of 1 placebo subject).

Anaesthetic complications
Anaesthetic complications identified in any subject who received any dose of Bridion plus a NMBA included the following:

- Anaesthetic complication (3%, 57 subjects),
- Airway complication of anaesthesia (1%, 12 subjects),
- Delayed recovery from anaesthesia (< 1%, 5 subjects),
- Unwanted awareness during anaesthesia (< 1%, 2 subjects)
- Anaesthetic complication cardiac (< 1%, 1 subject).

Most anaesthetic complications and coughing were reported in fentanyl and propofol treated subjects and not in subjects administered remifentanil or sevoflurane.

Approximately half of the anaesthetic complications (28/63) are considered to be inadequate (light) anaesthesia. Most complications were associated with immediate reversal at recovery to a TOF-ratio of 0.9, i.e. at restoration of neuromuscular blocking function.

Airway complication of anaesthesia
This includes descriptions such as bucking and spontaneous breathing. In Phase 1-3 trials with a placebo group, the incidence of airway complication of anaesthesia was 1% in Bridion subjects 0% in placebo subjects. In two Phase 3 controlled trials (19.4.301 and 19.4.302) airway complication of anaesthesia occurred more frequently in neostigmine subjects (2%) compared to Bridion subjects (1%).

Airway complication of anaesthesia was judged to be related to treatment with Bridion in < 1% (3 subjects) of all Bridion subjects i.e., in about 25% of all subjects who experienced the AE. Most occurrences of airway complication of anaesthesia were mild to moderate; a severe occurrence was reported in only 1 (< 1%) of all Bridion subjects.

Anaesthetic complication
This PT includes verbatim descriptions such as movement (of a limb or the body) or coughing during the anaesthetic procedure or during surgery, grimacing, or suckling on the endotracheal tube. In the Phase 1-3 trials with a placebo group, the incidence of anaesthetic complication in Bridion subjects (8%) was more than twice the incidence in placebo subjects (1%), and a dose trend was observed. This AE was not observed in the Phase 3 controlled trials 19.4.301 and 19.4.302 in which Bridion was compared to neostigmine.

Anaesthetic complication was judged to be related to treatment with Bridion in about 1% of all Bridion subjects i.e., in about 40% of all subjects who experienced the AE, compared to neither of the 2 placebo subjects with this AE. Most occurrences of anaesthetic complication were mild to moderate; severe occurrences were reported in only 2 (< 1%) of all Bridion subjects. This AE occurred predominantly in trials in which Bridion was administered while anaesthesia was continued, and could have been caused by the fact that when removing one of the pillars of balanced anaesthesia the level of anaesthesia might not have been deep enough.

Delayed recovery from anaesthesia
This description includes terms such as delayed awakening from anaesthesia or extended recovery from anaesthesia. In Phase 1-3 trials with a placebo group, the incidence of delayed recovery from anaesthesia was 1% in Bridion subjects and 0% in placebo subjects. There was a low overall number of delayed recovery from anaesthesia (n=5). This AE was not observed in the controlled trials 19.4.301 and 19.4.302 in which Bridion was compared to neostigmine. Delayed recovery from anaesthesia led to the discontinuation of 1 of the 5 Bridion subjects. It was judged to be related to treatment with Bridion. All occurrences were mild to moderate in intensity.

Unwanted awareness during anaesthesia
The descriptions included “awareness during anaesthesia” and “awake” during anaesthesia. Two Bridion subjects but none in the placebo subjects experienced unwanted awareness during anaesthesia. Both occurrences were mild in intensity, and one was considered to be related to treatment with Bridion (16 mg/kg) by the investigator. The related event occurred in one subject and led to the subject’s discontinuation from the trial. The related AE started 26 minutes after Bridion administration and lasted one minute.

Residual blockade or reoccurrence of the block
The AE prolonged neuromuscular block, which includes verbatim terms of reoccurrence of blockade, residual blockade, insufficient curarization, and delayed recovery from neuromuscular block, was reported in 6 (< 1%) Bridion subjects overall and in no placebo subjects, and 4 (5%) neostigmine with vecuronium subjects in the Phase 3 controlled studies 19.4.301 and 19.4.302. All occurrences were mild to moderate in intensity. This AE was considered to be treatment-related by the investigator in 3 of the 6 Bridion subjects and in 2 of the 4 neostigmine with vecuronium subjects and it led to the discontinuation of one Bridion subject.

A total of 24 total Bridion subjects (NMBA was rocuronium, vecuronium, or pancuronium) had evidence of reoccurrence of blockade or residual blockade based on the TOF Watch® SX measurements during the period of neuromuscular monitoring. Four of the 24 Bridion subjects and an additional 2 Bridion subjects had clinical evidence of reoccurrence of blockade or residual blockade at recovery.

In the pooled Phase 1-3 studies with a placebo group, where the NMBA was rocuronium or vecuronium and where doses of Bridion ranged from < 2 mg/kg to 16 mg/kg, 11 (2%) Bridion subjects and no placebo subject had evidence of reoccurrence of blockade or residual blockade during the period of neuromuscular monitoring. In these studies, a higher percentage of Bridion subjects had evidence of reoccurrence of blockade or residual blockade during neuromuscular monitoring after receiving vecuronium (4%) than after receiving rocuronium (1%). One of the 11 Bridion subjects (rocuronium and 0.5 mg/kg Bridion) also had clinical evidence of reoccurrence of blockade or residual blockade at recovery, described as being unable to lift her head for more than 3 sec upon arrival in the recovery room.

Population PK-PD model investigating the re-use situation
To address clinical questions such as the clinical situation during which rocuronium would be required for reintubation following a previous administration of Bridion, the re-use situation, the applicant has used PK-PD simulations.

No formal clinical study has been conducted evaluating the reuse situation of rocuronium. For the reuse of vecuronium neither clinical study nor a simulation has been performed.

On the basis of the PK-PD simulation the applicant initially proposed a table to be included in the SPC, with recommended waiting times after different Bridion doses, for the readministration of rocuronium and vecuronium in patients with normal renal function and impaired renal function. This was not considered acceptable as the risk for misinterpretations and dosing errors was imminent. Following the responses to the LoQ a waiting time of 24 hours is recommended in the SPC if re-administration of rocuronium or vecuronium is required. If neuromuscular blockade is required before the recommended waiting time has passed, a nonsteroidal neuromuscular blocking agent should be used.

Immunological events
Only one dermatitis contact (< 1% Bridion, 0% placebo), occurred in Phase 1-3 studies in the placebo group. Two hypersensitivity reactions to Bridion (1% Bridion, 0% placebo), occurred in the pooled Phase I studies where subjects were not under anaesthesia and received no NMBA. This AE was reported in two subjects in trial 19.4.105 who received 32 mg/kg Bridion.

None of the allergic reactions (dermatitis contact, pruritus allergic, drug hypersensitivity, transfusion reaction, or hypersensitivity) were SAEs or led to the discontinuation of the trial. However, one phase 1 subject had a documented hypersensitivity reaction to Bridion. This subject discontinued the infusion of Bridion due to multiple AEs including paraesthesia, tachycardia, nausea, palpitations, stomach discomfort, dysgeusia, visual disturbances, flushing, and rash erythematous. A slight increase in serum tryptase, suggestive of possible allergic reaction aetiology was found. As a follow-up, skin and intracutaneous tests were conducted. This subject fulfilled the criteria for a sensitive subject in the skin prick test.

Since this was the first exposure to Bridion, it was thought that this subject was probably sensitized to Bridion by previous exposure to another compound with structural resemblance. The possibility of cross sensitization between Bridion and betalactam antibiotics was considered. The subject showed no sensitization to beta-lactam antibiotics in this test.

Another subject experienced a hypersensitivity reaction to Bridion in the thorough QTc trial 19.4.105. This trial was conducted with two doses of Bridion, 4 mg/kg and 32 mg/kg. During the last period of this trial, female subject with known allergy to penicillin since showed signs of a hypersensitivity

reaction. Approximately 1 min after start of infusion of 32 mg/kg Bridion, the subject developed paraesthesia in arms and legs, feeling of warmth in arms and legs, dizziness, feeling of narrow throat, breathing difficulties, tachycardia, and flushing. These symptoms lasted for one to two minutes and resolved with no treatment. All vital signs measured within the following 12 min were within normal limits. Approximately 1.5 hr after start of infusion the subject developed a rash on both forearms, which lasted approximately 1.25 hr and disappeared without treatment. Her serum total IgE was measured and was found to be within normal limits. Before this period, the subject experienced diarrhoea, single pustules on the breast, back and face, and itching after the previous administration of 4 mg/kg Bridion. In the other periods the subject showed no signs that might be the result of a hypersensitivity reaction.

Four other subjects in trial 19.4.105 also showed signs of possible hypersensitivity to Bridion. These alleged hypersensitivity reactions could have been caused by materials used during the procedure (e.g., latex, infusion lines, placebo) or the trial medication Bridion. Also a cross sensitivity between antibiotics and Bridion can not be ruled

In conclusion, a total of seven subjects in the clinical trials were identified with clinical symptoms which may have been indicative for hypersensitivity to Bridion. Two cases of positive intradermal testing to Bridion have been identified. According to the Applicant, the other test may indicate a false positive outcome but this could be excluded by a negative control (saline solution) in the intradermal test. At present there is no indication from clinical data or from literature for cross sensitization by other cyclodextrins or by antibiotics with structural similarity with Bridion. Pharmacovigilance will be required for detection of rare adverse events such as hypersensitivity reactions.

- Serious adverse events (SAE)/deaths/other significant events

Of a total of 135 SAEs in all the clinical trials, 122 occurred after the administration of the product. There were no deaths (and not in the ongoing studies either), and only 8 SAEs were considered related, by both the investigator and Organon. One SAE occurred in a placebo-treated patient. The remaining SAEs were 3 cases of QT-interval prolonged (+ one after placebo), hypotension, breathlessness on day after the administration, and two cases of bronchospasm. The case of hypotension occurred 5-10 minutes after the administration of the IP, and 2-5 minutes after a propofol and fentanyl bolus. The patient suffering from hypotension was later diagnosed to have respiratory failure and atrial fibrillation. The patients, who experienced bronchospasms, when extubated, had asthma in their medical history; the bronchospasms were thought to mostly relate to that, and also to the extubation itself.

A similar percentage of Bridion subjects (6%) and placebo subjects (4%) experienced at least one SAE. Those SAEs that occurred in more than one subject per group included electrocardiogram QT corrected (2% 15 subjects with Bridion and 1% 2 subjects with placebo) and small intestinal perforation (< 1%, 2 subjects with Bridion, and no placebo subject). Due to the relatively low number of SAEs, it is difficult to judge whether the incidence of SAEs was influenced by the type of NMBA used. All SAEs of electrocardiogram QT corrected (in both treatment groups) are only in subjects who received rocuronium because ECGs were not recorded in the three trials that used vecuronium as the NMBA (19.4.207, 19.4.208A, and 19.4.208B).

One subject suffered from cardiac arrest after administration of Bridion. A severe oculocardiac reflex, due to pressure of the eye bulbus during the surgery was considered to be the reason for asystole. The subject recovered from the SAE.

In a small, uncontrolled study, the Bridion with pancuronium group experienced SAEs in 2 (11%) subjects, which included abdominal abscess, candidiasis, and small intestinal perforation. None was considered related to the trial medication per the investigator.

Related (judged by the investigator) SAEs were reported in 1% of each treatment group (in 4 Bridion subjects, and in 1 placebo subject). In each of these cases, the sponsor judged the SAE to be unlikely related Bridion or not related to placebo medication.

Phase 1-3 trials, Bridion vs. Neostigmine
In the controlled Phase 3 trials 19.4.301 and 19.4.302, the incidence of SAEs was similar for Bridion (3%) and neostigmine (4%). Serious adverse events most frequently (incidence ≥ 2%) were found in the injury, poisoning, and procedural complications class (2% Bridion, 2% neostigmine) and in the gastrointestinal disorders class (2% Bridion, 0% placebo). Individual SAEs most often occurred in only one subject in a treatment group. Only two, post procedural haemorrhage and procedural complication, occurred in more than one subject per group.

Due to the relatively low number of SAEs, it is difficult to judge whether the incidence of SAEs was influenced by the type of NMBA administered. None of the SAEs in these trials was considered to be related to the trial medication by the investigator.

Phase 1 trials
There were no SAEs in the Phase 1 trials.

There were few cases where the recovery was slow, or there was evidence of re-occurrence of neuromuscular blockade, mostly, but not entirely, in patients treated with doses <2 mg/kg. Two of the cases occurred with 2 mg/kg, and 2 patients in the group 16mg/kg, but without any clinical signs. Theoretically a re-occurrence can happen also because of replacement interaction.

Phase 1 - 3 Dose Response
Overall, 6% of all subjects exposed to any dose of Bridion with a NMBA (rocuronium, vecuronium, or pancuronium) experienced at least one SAE. No dose response was apparent for the overall incidence of SAEs. The overall incidence of SAEs was 7% in the 2 mg/kg group, 5% in the 4 mg/kg group, and 5% in the 16 mg/kg group. Related SAEs (in the investigator's opinion) were reported in 7 Total Bridion subjects (in < 1% of the Total Bridion group). In each of these cases, the sponsor judged the SAE to be unlikely related.

The related (per the investigator) SAEs in Bridion subjects included the following:
- Electrocardiogram QT corrected interval prolonged (one 2 mg/kg subject and one 4 mg/kg subject),
- Bronchospasm (two 4 mg/kg subjects),
- Electrocardiogram QT prolonged (one 4 mg/kg subject),
- Respiratory failure (one < 2 mg/kg subject),
- Hypotension (one 3 mg/kg subject), and
- Atrial fibrillation (one < 2 mg/kg subject).

- Laboratory findings

In general there were no major findings in laboratory values or vital signs. In response to the LoQ the Applicant has provided data on biomarkers of renal proximal tubular toxicity and haemostasis. These as well as the clinical data available do not indicate association of Bridion with renal damage or haemostatic complications.

- Safety in special populations

Paediatric patients
Trial 19.4.306 was a Phase 3 trial to explore the efficacy, safety, and pharmacokinetics of Bridion in paediatric and adult subjects. A total of 91 subjects (8 infants, 24 children, 31 adolescents, and 28 adults) received a single, bolus, intravenous dose of Bridion (0.5, 1, 2, or 4 mg/kg) or placebo. Bridion was well tolerated by both paediatric and adult subjects. There were no readily apparent differences in the safety profile of Bridion among the age groups. There were no deaths or discontinuations due to an AE in any age group. Major safety findings for each age group are summarized below.

Infants & toddlers (28 days old - 23 months old): 6 Bridion, 2 placebo
A total of 7 of 8 infants (89%) experienced at least one treatment-emergent AE; 5 of 6 (83%) Bridion subjects and 2 of 2 (100%) placebo subjects. There was no dose response for the overall incidence of AEs (two 0.5 mg/kg subjects, one 1 mg/kg subject, one 2 mg/kg subject, one 4 mg/kg subject). No infant experienced an AE of severe intensity.

The most frequently reported AE was vomiting in two (33%) Bridion subjects and one (50%) placebo subject). The remaining AEs were each reported in one subject, and included gastroenteritis viral, nasopharyngitis, and hypoglycaemia in Bridion subjects, and pyrexia, rhinitis, and procedural complication in placebo subjects.

There was one investigator-reported drug-related AE, and a procedural complication in a placebo subject, that was described as *"bradycardia 2 min after IP injection (surgery related) (e.g. vagal stimulation)"*. One SAE was reported, for 0.5 mg/kg Bridion subject (vomiting for three days in the post-operative period, coded to PT gastroenteritis viral). The subject recovered, and the SAE was not related to the trial medication according to the investigator. The 0.5 mg/kg subject with the AE of hypoglycaemia had a markedly abnormal value for fasting serum glucose value of 1.39 mmol/L during the 60 min post-dose assessment.

Children (2-11 years old): 20 Bridion, 4 placebo
A total of 15 of 24 children (63%) experienced at least one AE; 12 of 20 (60%) Bridion subjects, and 3 of 4 (75%) placebo subjects. There was no dose response for the overall incidence of AEs (four 0.5 mg/kg subjects, two 1 mg/kg subjects, two 2 mg/kg subjects, four 4 mg/kg subjects). Two children experienced an AE of severe intensity (one subject in the 0.5 mg/kg Bridion group, and one subject in the 4.0 mg/kg Bridion dose group).

The most frequently reported AEs included vomiting 9 Bridion subjects (45%), and 2 placebo subjects (50%), and procedural pain six (30%) Bridion subjects, and 1 placebo subject (25%). The remaining AEs occurred only in Bridion subjects and included constipation, pain, and anaemia postoperative in two (10%) subjects each, and nausea, gastroenteritis viral, anxiety, dysuria, urinary retention, scrotal oedema, and pruritus in one (5%) subject each.

There was one investigator-reported drug-related AE, mild vomiting in a 2 mg/kg Bridion subject. One SAE was reported, for one subject who received 4 mg/kg Bridion (diarrhoea, haematuria with vesical clots, fever, weight loss, and oliguria, coded to PT gastroenteritis viral). The subject recovered, and the SAE was judged as not related to the trial medication according to the investigator. One 4 mg/kg subject with the AE of anaemia postoperative had a markedly abnormal value for haemoglobin on the morning of the post-operative day (value of 9.4 g/dL, safety range: 9.5 - 20 g/dL).

Adolescents (12-17 years old): 25 Bridion, 6 placebo
A total of 21 of 31 adolescents (68%) experienced at least one AE; 16 of 25 (64%) Bridion subjects and 5 of 6 (83%) placebo subjects. There was no dose response for the overall incidence of AEs (three 0.5 mg/kg subjects, three 1 mg/kg subjects, five 2 mg/kg subjects, five 4 mg/kg subjects). One adolescent subject (in the placebo group) experienced an AE of severe intensity.

The most frequently reported AEs included procedural pain in 11 Bridion subjects (44%) and in 3 placebo subjects (50%), vomiting in 6 Bridion subjects (24%) and in 3 placebo subjects (50%), and nausea in 5 Bridion subjects (20%), and 1 placebo subject (17%). The remaining AEs were each reported in one subject. These included pharyngitis, postoperative fever, procedural hypotension, oxygen saturation decreased, muscle spasms, pain in extremity, dizziness, headache, paraesthesia, and hot flush in Bridion subjects, and post procedural complication, hypoaesthesia, and excitability in placebo subjects.

There were four AEs considered to be drug-related by the investigator. These were vomiting (2 ml/kg Bridion), muscle spasms (0.5 mg/kg Bridion), paraesthesia (1 mg/kg Bridion), and hot flush (2 mg/kg Bridion). No SAEs occurred in this age group.

Adults (18-65 years old: 22 Bridion, 6 placebo)
A total of 16 of 28 adults (57%) experienced at least one AE; 13 of 22 (59%) Bridion subjects, and 3 of 6 (50%) placebo subjects. There was no dose response for the overall incidence of AEs one 0.5 mg/kg subject, five 1 mg/kg subjects, four 2 mg/kg subjects, three 4 mg/kg subjects. One adult subject in the placebo group experienced an AE of severe intensity.

The most frequently reported AEs were procedural pain in 5 Bridion subjects (23%) and in 1 placebo subject (17%), pruritus generalized in 2 Bridion subjects (9%) and in 1 placebo subject (17%), and constipation in 1 Bridion subject (5%) and in 1 placebo subject (17%). The remaining AEs were each reported in one subject. These included hyperthermia, pyrexia, ankle fracture, haematuria traumatic, wrist fracture, decreased appetite, hyperglycaemia, hyperkinesia, anxiety, and sleep disorder in Bridion subjects, and pain in one placebo subject.

One AE was considered to be drug-related by the investigator; this was decreased appetite in 2 mg/kg subject. No SAEs occurred in this age group. The 4 mg/kg subject with the AE of hyperglycaemia had markedly abnormal values for fasting serum glucose measured during the baseline, 60 min post-dose assessment, and the post-trial assessment. All reported values were above the upper limit of the safety range.

Overall, the product seems to be well tolerated by the paediatric patients. However, the number of patients studied is rather small. More data are expected as the Applicant submitted a Paediatric Investigation Plan in January 2008.

Patients with renal insufficiency
Subjects with normal or impaired renal function were studied because Bridion is predominantly cleared via the kidneys; therefore, renal impairment would be expected to increase subjects' exposure to Bridion and the NMBA. In Trial 19.4.304, renally-impaired subjects had a prolonged and 17-fold higher exposure to Bridion and a prolonged and 4-fold higher exposure to rocuronium compared to subjects with normal renal function. Nonetheless, the safety profiles between subjects with normal renal function vs. subjects with impaired renal function were not appreciably different. This is an important finding despite the fact that effective dialysis (using a high flux filter) of Bridion and rocuronium was not consistently demonstrated in Trial 19.4.304. The Applicant has committed to further investigate in patients with severe renal impairment and/or dialysis in the clinical trials studies 19.4.328 & 19.4.333 as stated in their letter of undertaking dated 28 May 2008.

Re-occurrence of neuromuscular blockade was not observed in study 19.4.304, in which 15 subjects with impaired renal function (CR_{CL} <30 ml/min) received 2.0 mg/kg Bridion. The Applicant argues that based on pharmacokinetics of Bridion and rocuronium, no additional risk of reoccurrence of blockade is expected in patients with severe renal insufficiency. The two clinical studies (19.4.328 and 19.44.333) planned will bring more information on the safety of Bridion in subjects with severe renal impairment. Currently the use of Bridion in patients with severe renal impairment is not recommended in the SPC. The metabolism and elimination of Bridion in patients undergoing haemodialysis or peritoneal dialysis is unclear. The Applicant has committed to study if Bridion can be removed by dialysis or other techniques in ICU patients (study protocol 19.4.333) as stated in their letter of undertaking dated 28 May 2008.

Patients with cardiac or pulmonary diseases
Overall, Bridion (at doses of 2.0 mg.kg-1 or 4.0 mg.kg-1) was shown to be both safe (and effective) in reversing a rocuronium-induced NMB when administered at the reappearance of T2 in subjects diagnosed with or without a history of pulmonary complication(s) or cardiac complication(s).

The paediatric, renally impaired, pulmonary impaired and cardiac patient populations are too limited that conclusions of the safety of Bridion can be made.

Bridion seems to cause hypotension in renally impaired patient population, bronchospasms in pulmonary impaired patient and QTc interval prolongations in cardiac patients. The QTc interval prolongation is discussed earlier in this assessment report.

The applicant was requested to clarify whether Bridion predisposes the patients to increased bleeding, also in these special patient populations. From non-clinical safety studies there is no indication of an increased risk for bleeding. Apart from non-clinical studies, haemostatic factors such as the laboratory parameters APTT and PT have not been studied in clinical trials. In order to get an indication whether

there are clinically relevant effects of Bridion on haemostatis, an analysis on relevant adverse events in clinical Phase 2-3 placebo-controlled studies was made. The combined rate for all types of haemorrhages in Bridion treated subjects was 5.7% (n = 649) and in placebo group 3.1% (n = 130). None of the individual AEs had a reporting rate of more than 1%. When limited to the more specific terms for surgery related bleedings, (Incision site haemorrhage, Post procedural haemorrhage, Haemorrhage and Operative Haemorrhage) the combined incidence was 2.8% in the total Bridion group. This is comparable to the 2.3% in the placebo group (no statistically significant difference). These rates are in line with the incidence of post-operative bleeding as reported in literature (0.2% - 4.7%). There appears to be no indication of clinically relevant effects of Bridion on haemostasis or for a haemolytic effect of Bridion. The effect of Bridion on coagulation will be further investigated in study 19.4.115 (CTA submitted Jan 2008) as stated in their letter of undertaking dated 28 May 2008. Although the frequency of bleeding complications in the placebo and Bridion are comparable, the Applicant's initiative for a clinical trial to further investigate the effects of Bridion on *in vitro* tests and *in vivo* was supported.

- Safety related to drug-drug interactions and other interactions

Effect of concomitant magnesium and antibiotics on adverse events incidence was explored:

- intravenous magnesium (which can potentiate neuromuscular blockade); and
- perioperative antibiotics (which can potentiate neuromuscular blockade).

The main purpose of this exploratory analysis was to compare the incidence of AEs suggestive of reoccurrence of blockade or residual blockade in subjects who did and did not receive these concomitant medications.

Phase 1 – 3 trials

For the Phase 1-3 trials, the analysis focuses on the largest Bridion group (N=1713) to increase the possibility of detecting a difference between those who did and did not receive the concomitant medication. The data for the placebo and neostigmine groups do not contribute significantly to this exploratory analysis. These groups are very small (N=140 placebo, N=167 neostigmine) in comparison to the Total Bridion group.

Of the 1713 subjects who received Bridion plus an NMBA, the following numbers of subjects received or did not receive intravenous magnesium, or perioperative antibiotics:

- Intravenous magnesium: 67 yes, 1646 no and
- Perioperative antibiotics: 236 yes, 1477 no.

The AE neuromuscular block prolonged did not occur more frequently in subjects who received these concomitant medications compared to those who did not receive them:

- Intravenous magnesium: 0 (0%) yes, 6 (< 1%) no;
- Perioperative antibiotics: 1 (< 1%) yes, 5 (< 1%) no.

In addition, only one of the 24 subjects who experienced reoccurrence of blockade or residual blockade - subject 204104007, who received intravenous magnesium at a dose level known to interfere with NMBAs as well as cefazolin sodium.

Also, concomitant antibiotics were recorded for only 7 of the 24 subjects. Six of the subjects received cephalosporins and two received penicillins. Potential drug interactions with Bridion were identified by the investigators in three subjects. Each of these subjects received 2 mg/kg Bridion. After careful consideration, the sponsor concluded that these reported potential interactions were not clinically relevant.

Phase 1 trials

An integrated analysis was not performed for the pooled phase 1 trials because these subjects did not receive an NMBA, and because concomitant medication use was generally prohibited. From extensive nonclinical trials, it was concluded that no clinically relevant interactions (either complexation and subsequent altered pharmacokinetics or pharmacodynamics, or displacement of the NMBA) would be expected with several drugs which are used during anaesthesia or during emergency treatment. In

addition, from the toxicology trials there were no indications suggesting that the potential complexation of endogenous molecules resulted in adverse effects. Nevertheless, for most studies the investigators were asked to record potential drug interactions with Bridion in the CRF (Case Report Form).

- Discontinuation due to adverse events

Phase 1 - 3 trials, Bridion vs. placebo
One (< 1%) Bridion subject (with rocuronium) and no placebo subject withdrew from a trial due to an AE (unwanted awareness during anaesthesia). The investigator considered this AE related to the trial medication. No subject who received Bridion and pancuronium withdrew from the trial due to an AE.

Phase 1 - 3 trials, Bridion vs. neostigmine
One (< 1%) neostigmine subject (with rocuronium) withdrew from a trial due to multiple AEs that were considered to be unrelated to the trial medication by the investigator. No Bridion subject withdrew from a trial due to an AE.

Phase 1 - 3, dose response studies
Four (< 1%) of all subjects who received Bridion and a NMBA withdrew from a trial due to an AE. Two subjects were in the <2 mg/kg group, one was in the 4 mg/kg group, and one was in the 16 mg/kg group. The most frequent AE leading to trial discontinuation was prolonged neuromuscular block (2 subjects in the <2 mg/kg group). Adverse events leading to trial discontinuation that were considered by the investigator to be related to treatment with Bridion included unwanted awareness during anaesthesia (one 16 mg/kg subject) and neuromuscular block prolonged (one < 2 mg/kg subject).

Phase 1 Trials
Trial 19.4.108: The infusion of the trial medication (Bridion) was not discontinued in any subject, and no subject withdrew from the trial due to an AE.

In the subset of pooled Phase 1 trials, the concept of 'discontinuation of trial medication due to AE' is applicable only to the trials 19.4.105 and 19.4.106 in which the trial medication was infused over 2 minutes and 5 minutes (respectively). Other data presented in this section represent subject withdrawal from the trial due to an AE.

Bridion vs. Placebo and Pooled Phase 1 Dose Response
Three (1%) Total Bridion subjects and no placebo subject discontinued a trial due to an AE. All AEs resolved without treatment, and were considered to be related to the administration of Bridion by both the investigator and the sponsor. This AE is discussed further under "allergic reaction"

In conclusion, a limited number of discontinuations due to the AEs were reported. Bridion seems to be rather well tolerated.

- Post marketing experience

There is currently no post marketing experience with Bridion.

- Discussion on clinical safety

Bridion seems to be well tolerated in the studied patient population. The most common adverse events were procedural pain, injection site complications, and postoperative nausea. In Phase 1 studies, the volunteers studied complained about injection site irritation and dysgeusia.

The anaesthetic complications include movement (of a limb or the body) or coughing during the anaesthetic procedure or during surgery, grimacing, or suckling on the endotracheal tube, airway complication in anaesthesia, delayed recovery, unwanted awareness during anaesthesia. Awareness during anaesthesia occurred in two patients, and caused one patient to discontinue the study.

The incidence of anaesthetic complications in the Phase 1-3 trials (with a placebo group) in Bridion subjects (8%) was higher than the incidence in placebo subjects (1%), and a dose trend was observed. This AE was not observed in the Phase 3 controlled trials 19.4.301 and 19.4.302 in which Bridion was

compared to neostigmine. Signs of inadequate anaesthesia were movement during anaesthesia/surgery and sucking the endotracheal tube. In response to the LoQ, the Applicant has evaluated all cases of anaesthetic complications and it was concluded that the cases can be considered as inadequate (light) anaesthesia or were associated with immediate reversal at recovery to a TOF-ratio of 0.9, i.e. at restoration of neuromuscular blocking function.

The QTc interval prolongation is of concern. Abnormally prolonged QTc interval may lead to *torsades des pointes*, a life threatening arrhythmia. There were significant prolongations in the QTc interval in all of the Phase 1-3 studies. Especially, the use of sevoflurane increased the incidence of abnormally long QTc intervals but prolongations were also observed with the use of propofol. Follow up measures on QT prolongation are planned and the applicant has committed to provide detailed evaluation of the QTc prolongations reported as SAEs in the clinical trials - particularly related to concomitant administered drugs (sevoflurane, propofol), as a post-authorisation commitment, as stated in their letter of undertaking dated 28 May 2008. The Applicant should also closely follow and report the QTc interval prolongations in PSURs.

In addition, the suspected cases of re-occurrence of neuromuscular blockade have been evaluated in detail following the responses to the LoQ. It was concluded that the risk of reoccurrence at doses recommended is very low and adequate warnings have been included in the SPC.

2.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system
The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country..

Risk Management Plan

The MAA submitted a risk management plan.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Table Summary of the risk management plan

Important identified risks		
Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Delayed onset time or insufficient neuromuscular blockade at re-treatment with steroidal neuromuscular blocking agent	Routine pharmacovigilance	• Warning in Section 4.4 of the SmPC that if re-administration with rocuronium or vecuronium is required after reversal with sugammadex, waiting time of 24 hours is recommended. • Warning in Section 4.4 of the SmPC that if neuromuscular blockade is required before the recommended waiting time has passed, a non-steroidal neuromuscular blocking agent should be used.

Neuromuscular block prolonged (Delayed recovery)	Routine pharmacovigilance	• Section 4.2 of the SmPC recommends the use of appropriate neuromuscular monitoring and includes detailed dosing information for routine and immediate reversal, depending on level of blockade. • Section 4.2 of the SmPC indicates that reversal may be delayed in elderly but that no dose adjustment is required. • Warning in section 4.4 of the SmPC that conditions associated with prolonged circulation time or oedematous state may be associated with longer recovery time. • Warning in section 4.5 of the SmPC that for toremifene, some displacement of vecuronium or rocuronium from the complex with sugammadex could occur. • Warning in section 4.5 of SmPC that a high dose of flucloxacillin (infusion of 500 mg or more) or fusidic acid might cause some displacement of rocuronium or vecuronium from sugammadex.
Re-occurrence of neuromuscular blockade	Routine pharmacovigilance	• Section 4.2 of the SmPC recommends the use of appropriate neuromuscular monitoring and includes detailed dosing information for routine and immediate reversal, depending on level of blockade. • Section 4.2 of the SmPC regarding re-occurrence of blockade post-operatively and recommending a repeat dose of sugammadex. • Warning in section 4.4 of SmPC that ventilatory support is mandatory for patients until adequate spontaneous respiration is restored following reversal of neuromuscular blockade. • Warning in section 4.4 of SmPC that in clinical trials a re-occurrence of neuromuscular blockade was reported along with details of prevention. • Warning in section 4.4 of the SmPC that when drugs which potentiate neuromuscular blockade are used in the post-operative period, special attention should be paid to the possibility of re-occurrence of blockade.

Important identified risks		
Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Re-occurrence of neuromuscular blockade (continued)	Routine pharmacovigilance	• Warning in section 4.4 of the SmPC regarding displacement of rocuronium or vecuronium and the requirement for monitoring. • Warning in section 4.5 of the SmPC that a high dose of flucloxacillin (infusion of 500 mg or more) or fusidic acid might cause some displacement of rocuronium or vecuronium from sugammadex.
Anesthetic complication / Light anesthesia	Routine pharmacovigilance	• Warning in section 4.4 of SmPC that when neuromuscular blockade was reversed intentionally in the middle of anaesthesia in clinical trials, signs of light anaesthesia were noted occasionally
Use of sugammadex in patients with renal impairment	Conduct two studies in severe renal impaired patients. One study in ICU patients to investigate the dialysis of sugammadex and one study to investigate the safety after 4 mg/kg sugammadex.	• Information in section 4.2 of the SmPC concerning mild and moderate renal impairment • Warning in section 4.4 in the SmPC regarding use in patients with severe renal failure • Warning in section 4.4 in the SmPC regarding re-administration with neuromuscular blocking agents in patients with mild to moderate impaired renal function
Important potential risks		
Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Drug hypersensitivity	Routine pharmacovigilance	• Contraindication in section 4.3 when the patient has a hypersensitivity to the active substance or to any of the excipients. • Warning in section 4.4 of SmPC that clinicians should be prepared for the possibility of these reactions and take the necessary precautions • Allergic-like reactions labelled in section 4.8 of the SmPC
Capturing Interactions	Routine pharmacovigilance	• Warning in section 4.5 of SmPC regarding interactions with progestogens and estrogens and effects on contraception. • Warning in section 4.4 of SmPC that certain drugs could become less

		effective due to a lowering of the (free) plasma concentrations.
Displacement interactions	Routine pharmacovigilance	• Information in section 4.2 of the SmPC that in the exceptional situation of re-occurrence of blockade post-operatively a repeat dose of sugammadex is recommended. • Warning in section 4.4 of the SmPC that rocuronium or vecuronium could be displaced and the requirement for monitoring. Warning in section 4.5 of
Important potential risks		
Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Displacement interactions (continued)	Routine pharmacovigilance	SmPC that a high dose of flucloxacillin (infusion of 500 mg or more) and intravenous administration of fusidic acid might cause some displacement of rocuronium or vecuronium and the requirement for monitoring. • Warning in section 4.5 of the SmPC that for toremifene, some displacement of vecuronium or rocuronium could occur.
Important missing data		
Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Effect on values for laboratory parameters of blood coagulation time (aPTT, PT (inr), PT)	Routine pharmacovigilance	Information in section 4.5 of the SmPC that sugammadex does in general not interfere with laboratory tests with the possible exception of some coagulation parameters [aPTT, PT and PT(inr)]
Exposure in infants and neonates	Studies in paediatric patients	• Information in section 4.2 of the SmPC on dose recommendations for children and adolescents (2-17 years) • Information in section 4.2 of the SmPC: use in neonates and infants is not recommended. • In section 6.6 of the SmPC dilution recommendations for paediatric patients are given.
Exposure in pregnancy	Routine pharmacovigilance	Information in section 4.6 of the SPC
Excretion of sugammadex in human milk	Routine pharmacovigilance	Information in section 4.6 of the SPC

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology
In summary, the safety margins of the compound are wide from the toxicology point of view. Non-clinical pharmacology, pharmacokinetics and toxicology have been adequately investigated.

However at present, no conclusions regarding environmental risks can be made. A number of issues remain to be addressed and the applicant has agreed to provide this information as a post-authorisation commitment, as stated in their letter of undertaking dated 28 May 2008.

Efficacy
The Applicant has demonstrated that sugammadex is selective for steroidal neuromuscular blocking agents. It rapidly encapsulates free steroidal NMBA, e.g. rocuronium and vecuronium, thereby preventing their pharmacological actions in the neuromuscular junction in a dose depending basic. Data provided indicates that the affinity of sugammadex for rocuronium > vecuronium>>pancuronium. However, sugammadex does not reverse neuromuscular block induced by succinylcholine or benzylisoquinolium compounds, and thus anticholinesterases are needed for reversal of benzylisoquinolone-induced NMB.

Safety
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 have adequately addressed these.

- User consultation

The PL user consultation included in the original application is acceptable and no further PL testing is required.

Risk-benefit assessment
A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered consensus that the risk-benefit balance of Bridion in the 'Reversal of neuromuscular blockade induced by rocuronium or vecuronium' was favourable and therefore recommended the granting of the marketing authorisation.