Clinical trial results:
An Open-label, Randomized, Phase IIIB, Multicenter Trial to Evaluate the Pharmacodynamic Parameters of Intubation Bolus, and Bolus and Infusion Maintenance Doses of Zemuron® in Pediatric and Adolescent Subjects

Summary

EudraCT number	2005-002926-67
Trial protocol	DE
Global end of trial date	05 September 2007

Results information

Result version number	v2 (current)
This version publication date	30 July 2016
First version publication date	05 March 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	P05797

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00124735
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration number: MK-8085-001, Organon Registration number: 021048

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 September 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to determine the dose requirements of Zemuron (rocuronium bromide) when administered as a bolus dose (a single, large dose) for intubation (insertion of a tube through the nose or mouth into the trachea to provide artificial ventilation) and when administered by either continuous infusion or bolus doses for maintenance of muscle relaxation in term neonates (birth to <28 days old), infants (28 days to ≤3 months old), toddlers (>3 months to ≤2 years of age), children (>2 years to ≤11 years of age), and adolescents (>11 years to ≤17 years of age).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Sevoflurane at 2.0-2.5 minimum alveolar concentration (MAC) to up to 7%-8% inspired concentration and nitrous oxide at 0%-70%, or propofol 1-3 mg/kg (may be used in neonates only) for induction of anesthesia; isoflurane 1.0±0.2% expired end-tidal concentration in 0%-70% nitrous oxide and, if needed, propofol as intermittent bolus dose(s) (0.5-2 mg/kg) or infusion (50–150 µg/kg/min) for maintenance of anesthesia.

Evidence for comparator: -

Actual start date of recruitment	01 October 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	United States: 133
Worldwide total number of subjects	149
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	12

Infants and toddlers (28 days-23 months)	52
Children (2-11 years)	49
Adolescents (12-17 years)	36
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 149 participants were enrolled and randomized in the trial, including 71 participants in the bolus maintenance group and 78 participants in the infusion maintenance group

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Zemuron Bolus Maintenance - Neonates

Arm description:

Neonate participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Arm type	Experimental
Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose, or 1.0 mg/kg bolus dose if had received propofol for anesthesia induction; For maintenance of muscle relaxation – initial 0.15 mg/kg bolus dose at reappearance of T3 (the third twitch of a Train of Four [TOF] stimulation) with additional bolus doses administered at the reappearance of T3 after previous bolus dose

Arm title	Zemuron Bolus Maintenance – Infants

Arm description:

Infant participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Arm type	Experimental
Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose; For maintenance of muscle relaxation – initial 0.15 mg/kg bolus dose at reappearance of T3 (the third twitch of a TOF stimulation) with additional bolus doses administered at the reappearance of T3 after previous bolus dose

Arm title	Zemuron Bolus Maintenance – Toddlers

Arm description:

Toddler participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Arm type	Experimental

Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose; For maintenance of muscle relaxation – initial 0.15 mg/kg bolus dose at reappearance of T3 (the third twitch of a TOF stimulation) with additional bolus doses administered at the reappearance of T3 after previous bolus dose

Arm title	Zemuron Bolus Maintenance – Children

Arm description:

Child participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Arm type	Experimental
Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose; For maintenance of muscle relaxation – initial 0.15 mg/kg bolus dose at reappearance of T3 (the third twitch of a TOF stimulation) with additional bolus doses administered at the reappearance of T3 after previous bolus dose

Arm title	Zemuron Bolus Maintenance – Adolescents

Arm description:

Adolescent participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Arm type	Experimental
Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose; For maintenance of muscle relaxation – initial 0.15 mg/kg bolus dose at reappearance of T3 (the third twitch of a TOF stimulation) with additional bolus doses administered at the reappearance of T3 after previous bolus dose

Arm title	Zemuron Continuous Infusion Maintenance - Neonates

Arm description:

Neonate participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Arm type	Experimental
Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose, or 1.0 mg/kg bolus dose if had received propofol for anesthesia induction; For maintenance of muscle relaxation – continuous infusion of 10 µg/kg/min beginning at reappearance of T2 (the second twitch of a TOF stimulation), infusion was to be adjusted approximately 2.0-5.0 µg/kg/min every 3 minutes until one or two twitches were maintained

Arm title	Zemuron Continuous Infusion Maintenance - Infants

Arm description:

Infant participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Arm type	Experimental
Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose; For maintenance of muscle relaxation – continuous infusion of 10 µg/kg/min beginning at reappearance of T2 (the second twitch of a TOF stimulation), infusion was to be adjusted approximately 2.0-5.0 µg/kg/min every 3 minutes until one or two twitches were maintained

Arm title	Zemuron Continuous Infusion Maintenance - Toddlers

Arm description:

Toddler participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Arm type	Experimental
Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose; For maintenance of muscle relaxation – continuous infusion of 10 µg/kg/min beginning at reappearance of T2 (the second twitch of a TOF stimulation), infusion was to be adjusted approximately 2.0-5.0 µg/kg/min every 3 minutes until one or two twitches were maintained

Arm title	Zemuron Continuous Infusion Maintenance - Children

Arm description:

Child participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Arm type	Experimental
Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose; For maintenance of muscle relaxation – continuous infusion of 10 µg/kg/min beginning at reappearance of T2 (the second twitch of a TOF stimulation), infusion was to be adjusted approximately 2.0-5.0 µg/kg/min every 3 minutes until one or two twitches were maintained

Arm title	Zemuron Continuous Infusion Maintenance - Adolescents

Arm description:

Adolescent participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Arm type	Experimental

Investigational medicinal product name	Zemuron
Investigational medicinal product code	
Other name	Esmeron, rocuronium bromide, MK-8085, SCH 900085, Org 9426
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For intubation - 0.6 mg/kg bolus dose; For maintenance of muscle relaxation – continuous infusion of 10 µg/kg/min beginning at reappearance of T2 (the second twitch of a TOF stimulation), infusion was to be adjusted approximately 2.0-5.0 µg/kg/min every 3 minutes until one or two twitches were maintained

Number of subjects in period 1	Zemuron Bolus Maintenance - Neonates	Zemuron Bolus Maintenance – Infants	Zemuron Bolus Maintenance – Toddlers
Started	5	8	18
Treated	5	6	18
Completed	4	6	18
Not completed	1	2	0
Physician decision	1	-	-
Required tourniquet	-	-	-
Not treated	-	2	-
Protocol deviation	-	-	-

Number of subjects in period 1	Zemuron Bolus Maintenance – Children	Zemuron Bolus Maintenance – Adolescents	Zemuron Continuous Infusion Maintenance - Neonates
Started	21	19	7
Treated	18	17	5
Completed	18	17	5
Not completed	3	2	2
Physician decision	-	-	-
Required tourniquet	-	-	-
Not treated	3	2	2
Protocol deviation	-	-	-

Number of subjects in period 1	Zemuron Continuous Infusion Maintenance - Infants	Zemuron Continuous Infusion Maintenance - Toddlers	Zemuron Continuous Infusion Maintenance - Children
Started	6	20	25
Treated	6	19	23
Completed	6	19	22
Not completed	0	1	3
Physician decision	-	-	-
Required tourniquet	-	-	-
Not treated	-	1	2

Protocol deviation	-	-	1

Number of subjects in period 1	Zemuron Continuous Infusion Maintenance - Adolescents
Started	20
Treated	20
Completed	18
Not completed	2
Physician decision	-
Required tourniquet	2
Not treated	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Zemuron Bolus Maintenance - Neonates
Reporting group description:	
Neonate participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Bolus Maintenance – Infants
Reporting group description:	
Infant participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Bolus Maintenance – Toddlers
Reporting group description:	
Toddler participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Bolus Maintenance – Children
Reporting group description:	
Child participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Bolus Maintenance – Adolescents
Reporting group description:	
Adolescent participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Neonates
Reporting group description:	
Neonate participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Infants
Reporting group description:	
Infant participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Toddlers
Reporting group description:	
Toddler participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Children
Reporting group description:	
Child participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Adolescents
Reporting group description:	
Adolescent participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	

Reporting group values	Zemuron Bolus Maintenance - Neonates	Zemuron Bolus Maintenance – Infants	Zemuron Bolus Maintenance – Toddlers
Number of subjects	5	8	18
Age Categorical Units: Subjects			
≤18 years	5	8	18
Between 18 and 65 years	0	0	0
≥65 years	0	0	0

Gender Categorical Units: Subjects			
Female	2	1	1
Male	3	7	17

Reporting group values	Zemuron Bolus Maintenance – Children	Zemuron Bolus Maintenance – Adolescents	Zemuron Continuous Infusion Maintenance - Neonates
Number of subjects	21	19	7
Age Categorical Units: Subjects			
≤18 years	21	19	7
Between 18 and 65 years	0	0	0
≥65 years	0	0	0
Gender Categorical Units: Subjects			
Female	9	8	2
Male	12	11	5

Reporting group values	Zemuron Continuous Infusion Maintenance - Infants	Zemuron Continuous Infusion Maintenance - Toddlers	Zemuron Continuous Infusion Maintenance - Children
Number of subjects	6	20	25
Age Categorical Units: Subjects			
≤18 years	6	20	25
Between 18 and 65 years	0	0	0
≥65 years	0	0	0
Gender Categorical Units: Subjects			
Female	3	7	11
Male	3	13	14

Reporting group values	Zemuron Continuous Infusion Maintenance - Adolescents	Total	
Number of subjects	20	149	
Age Categorical Units: Subjects			
≤18 years	20	149	
Between 18 and 65 years	0	0	
≥65 years	0	0	
Gender Categorical Units: Subjects			
Female	12	56	
Male	8	93	

Subject analysis sets

Subject analysis set title	Zemuron Bolus Maintenance - Neonates
Subject analysis set type	Full analysis

Subject analysis set description:

Neonate participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Subject analysis set title	Zemuron Bolus Maintenance – Infants
Subject analysis set type	Full analysis

Subject analysis set description:

Infant participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Subject analysis set title	Zemuron Bolus Maintenance – Toddlers
Subject analysis set type	Full analysis

Subject analysis set description:

Toddler participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Subject analysis set title	Zemuron Bolus Maintenance – Children
Subject analysis set type	Full analysis

Subject analysis set description:

Child participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Subject analysis set title	Zemuron Bolus Maintenance – Adolescents
Subject analysis set type	Full analysis

Subject analysis set description:

Adolescent participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Neonates
Subject analysis set type	Full analysis

Subject analysis set description:

Neonate participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Infants
Subject analysis set type	Full analysis

Subject analysis set description:

Infant participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Toddlers
Subject analysis set type	Full analysis

Subject analysis set description:

Toddler participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Children
Subject analysis set type	Full analysis

Subject analysis set description:

Child participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Adolescents
Subject analysis set type	Full analysis

Subject analysis set description:

Adolescent participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Reporting group values	Zemuron Bolus Maintenance - Neonates	Zemuron Bolus Maintenance – Infants	Zemuron Bolus Maintenance – Toddlers
Number of subjects	5	6	18
Age Categorical Units: Subjects			
≤18 years	5	6	18

Between 18 and 65 years	0	0	0
≥65 years	0	0	0

Gender Categorical Units: Subjects			
Female	2	1	1
Male	3	5	17

Reporting group values	Zemuron Bolus Maintenance – Children	Zemuron Bolus Maintenance – Adolescents	Zemuron Continuous Infusion Maintenance - Neonates
Number of subjects	18	17	5
Age Categorical Units: Subjects			
≤18 years	18	17	5
Between 18 and 65 years	0	0	0
≥65 years	0	0	0
Gender Categorical Units: Subjects			
Female	8	6	2
Male	10	11	3

Reporting group values	Zemuron Continuous Infusion Maintenance - Infants	Zemuron Continuous Infusion Maintenance - Toddlers	Zemuron Continuous Infusion Maintenance - Children
Number of subjects	6	19	23
Age Categorical Units: Subjects			
≤18 years	6	19	23
Between 18 and 65 years	0	0	0
≥65 years	0	0	0
Gender Categorical Units: Subjects			
Female	3	6	11
Male	3	13	12

Reporting group values	Zemuron Continuous Infusion Maintenance - Adolescents		
Number of subjects	20		
Age Categorical Units: Subjects			
≤18 years	20		
Between 18 and 65 years	0		
≥65 years	0		
Gender Categorical Units: Subjects			
Female	12		
Male	8		

End points

End points reporting groups

Reporting group title	Zemuron Bolus Maintenance - Neonates
Reporting group description:	
Neonate participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Bolus Maintenance – Infants
Reporting group description:	
Infant participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Bolus Maintenance – Toddlers
Reporting group description:	
Toddler participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Bolus Maintenance – Children
Reporting group description:	
Child participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Bolus Maintenance – Adolescents
Reporting group description:	
Adolescent participants randomized to receive a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Neonates
Reporting group description:	
Neonate participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Infants
Reporting group description:	
Infant participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Toddlers
Reporting group description:	
Toddler participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Children
Reporting group description:	
Child participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Reporting group title	Zemuron Continuous Infusion Maintenance - Adolescents
Reporting group description:	
Adolescent participants randomized to receive a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation	
Subject analysis set title	Zemuron Bolus Maintenance - Neonates
Subject analysis set type	Full analysis
Subject analysis set description:	
Neonate participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Subject analysis set title	Zemuron Bolus Maintenance – Infants
Subject analysis set type	Full analysis
Subject analysis set description:	
Infant participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation	
Subject analysis set title	Zemuron Bolus Maintenance – Toddlers

Subject analysis set type	Full analysis

Subject analysis set description:

Toddler participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Subject analysis set title	Zemuron Bolus Maintenance – Children
Subject analysis set type	Full analysis

Subject analysis set description:

Child participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Subject analysis set title	Zemuron Bolus Maintenance – Adolescents
Subject analysis set type	Full analysis

Subject analysis set description:

Adolescent participants who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Neonates
Subject analysis set type	Full analysis

Subject analysis set description:

Neonate participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Infants
Subject analysis set type	Full analysis

Subject analysis set description:

Infant participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Toddlers
Subject analysis set type	Full analysis

Subject analysis set description:

Toddler participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Children
Subject analysis set type	Full analysis

Subject analysis set description:

Child participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Subject analysis set title	Zemuron Continuous Infusion Maintenance - Adolescents
Subject analysis set type	Full analysis

Subject analysis set description:

Adolescent participants who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Primary: Total Dose of Zemuron Administered

End point title	Total Dose of Zemuron Administered[1]

End point description:

Total Zemuron dose from administration of intubating dose to reappearance of T3 (the third twitch of a TOF stimulation) after the last maintenance bolus dose or discontinuation of Zemuron infusion. Analysis population is the Per Protocol group, which is all participants who were randomized after protocol Amendment 5 (major revision to study), received study drug, had at least one efficacy parameter measured and did not have any major protocol violations.

End point type	Primary

End point timeframe:

From administration of intubating dose of Zemuron through reappearance of T3 after last bolus maintenance Zemuron dose or end of continuous infusion maintenance Zemuron dose, an estimated average duration of 107 minutes

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical results are not presented due to extremely small sample sizes in many of the groups.

End point values	Zemuron Bolus Maintenance - Neonates	Zemuron Bolus Maintenance – Infants	Zemuron Bolus Maintenance – Toddlers	Zemuron Bolus Maintenance – Children
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	5	13	14
Units: mg/kg				
arithmetic mean (standard deviation)	0.91 (± 0.17)	0.78 (± 0.07)	0.86 (± 0.18)	0.81 (± 0.1)

End point values	Zemuron Bolus Maintenance – Adolescents	Zemuron Continuous Infusion Maintenance - Neonates	Zemuron Continuous Infusion Maintenance - Infants	Zemuron Continuous Infusion Maintenance - Toddlers
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	5	2	12
Units: mg/kg				
arithmetic mean (standard deviation)	0.96 (± 0.16)	1.01 (± 0.37)	0.84 (± 0.15)	1 (± 0.25)

End point values	Zemuron Continuous Infusion Maintenance - Children	Zemuron Continuous Infusion Maintenance - Adolescents		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	15		
Units: mg/kg				
arithmetic mean (standard deviation)	1.26 (± 0.78)	0.99 (± 0.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Recovery of T4/T1 (TOF Fourth Twitch to First Twitch) Ratio 70%

End point title	Duration of Recovery of T4/T1 (TOF Fourth Twitch to First Twitch) Ratio 70%

End point description:

The time it takes for the T4 to T1 ratio to reach 70%. The T4/T1 ratio is indicative of recovery. At complete recovery, the T4/T1 ratio is 1.0 (100%). Analysis population is the Per Protocol group, which is all participants who were randomized after protocol Amendment 5 (major revision to study), received study drug, had at least one efficacy parameter measured and did not have any major protocol violations. Also to be included, participant must have an evaluable assessment for this measure.

End point type	Secondary

End point timeframe:

After surgery, from the reappearance of T3 after Zemuron infusion/last bolus dose of Zemuron to T4/T1 ratio of 70%

End point values	Zemuron Bolus Maintenance - Neonates	Zemuron Bolus Maintenance – Infants	Zemuron Bolus Maintenance – Toddlers	Zemuron Bolus Maintenance – Children
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	4	10	12
Units: minutes				
arithmetic mean (standard deviation)	29.62 (± 13.6)	33.25 (± 16.17)	22.65 (± 7.62)	16.29 (± 6.98)

End point values	Zemuron Bolus Maintenance – Adolescents	Zemuron Continuous Infusion Maintenance - Neonates	Zemuron Continuous Infusion Maintenance - Infants	Zemuron Continuous Infusion Maintenance - Toddlers
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	3	1	9
Units: minutes				
arithmetic mean (standard deviation)	28.04 (± 13.33)	43.42 (± 1.53)	33.25 (± 0)	23.08 (± 13.4)

End point values	Zemuron Continuous Infusion Maintenance - Children	Zemuron Continuous Infusion Maintenance - Adolescents		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: minutes				
arithmetic mean (standard deviation)	18.32 (± 13.16)	27.59 (± 12.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Recovery of T4/T1 (TOF Fourth Twitch to First Twitch) Ratio 80%

End point title	Duration of Recovery of T4/T1 (TOF Fourth Twitch to First Twitch) Ratio 80%

End point description:

The time it takes for the T4 to T1 ratio to reach 80%. The T4/T1 ratio is indicative of recovery. At complete recovery, the T4/T1 ratio is 1.0 (100%). Analysis population is the Per Protocol group, which is

all participants who were randomized after protocol Amendment 5 (major revision to study), received study drug, had at least one efficacy parameter measured and did not have any major protocol violations. Also to be included, participant must have an evaluable assessment for this measure.

End point type	Secondary

End point timeframe:

After surgery, from the reappearance of T3 after Zemuron infusion/last bolus dose of Zemuron to T4/T1 ratio of 80%

End point values	Zemuron Bolus Maintenance - Neonates	Zemuron Bolus Maintenance – Infants	Zemuron Bolus Maintenance – Toddlers	Zemuron Bolus Maintenance – Children
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	9	11
Units: minutes				
arithmetic mean (standard deviation)	36.62 (± 17.14)	43.58 (± 21.47)	32.39 (± 12.84)	20.43 (± 9.79)

End point values	Zemuron Bolus Maintenance – Adolescents	Zemuron Continuous Infusion Maintenance - Neonates	Zemuron Continuous Infusion Maintenance - Infants	Zemuron Continuous Infusion Maintenance - Toddlers
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	3	1	9
Units: minutes				
arithmetic mean (standard deviation)	36.1 (± 20.45)	57.83 (± 12.33)	44.75 (± 0)	29.47 (± 16.65)

End point values	Zemuron Continuous Infusion Maintenance - Children	Zemuron Continuous Infusion Maintenance - Adolescents		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	11		
Units: minutes				
arithmetic mean (standard deviation)	21.84 (± 15.12)	35.45 (± 17.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Recovery of T4/T1 (TOF Fourth Twitch to First Twitch) Ratio 90%

End point title	Duration of Recovery of T4/T1 (TOF Fourth Twitch to First

	Twitch) Ratio 90%

End point description:

The time it takes for the T4 to T1 ratio to reach 90%. The T4/T1 ratio is indicative of recovery. At complete recovery, the T4/T1 ratio is 1.0 (100%). Analysis population is the Per Protocol group, which is all participants who were randomized after protocol Amendment 5 (major revision to study), received study drug, had at least one efficacy parameter measured and did not have any major protocol violations. Also to be included, participant must have an evaluable assessment for this measure.

End point type	Secondary

End point timeframe:

After surgery, from the reappearance of T3 after Zemuron infusion/last bolus dose of Zemuron to T4/T1 ratio of 90%

End point values	Zemuron Bolus Maintenance - Neonates	Zemuron Bolus Maintenance – Infants	Zemuron Bolus Maintenance – Toddlers	Zemuron Bolus Maintenance – Children
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	8	8
Units: minutes				
arithmetic mean (standard deviation)	28.25 (± 0)	53.66 (± 14.58)	43.31 (± 18.2)	23.09 (± 10.9)

End point values	Zemuron Bolus Maintenance – Adolescents	Zemuron Continuous Infusion Maintenance - Neonates	Zemuron Continuous Infusion Maintenance - Infants	Zemuron Continuous Infusion Maintenance - Toddlers
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	1	1	9
Units: minutes				
arithmetic mean (standard deviation)	51.79 (± 33.97)	52.25 (± 0)	50.75 (± 0)	37.86 (± 18.46)

End point values	Zemuron Continuous Infusion Maintenance - Children	Zemuron Continuous Infusion Maintenance - Adolescents		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	10		
Units: minutes				
arithmetic mean (standard deviation)	28.46 (± 22.35)	38.68 (± 16.08)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For non-serious adverse events (AEs), through in-trial period, which ends at stable neuromuscular recovery (up to 90% of T4/T1 ratio) or administration of another muscle relaxant or a reversal agent. For serious AEs, up to 7 days post-surgery

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Zemuron Continuous Infusion Maintenance

Reporting group description:

Participants in all age groups combined who received a bolus dose of Zemuron for intubation followed by continuous infusion of Zemuron for maintenance of muscle relaxation

Reporting group title	Zemuron Bolus Maintenance

Reporting group description:

Participants in all age groups combined who received a bolus dose of Zemuron for intubation followed by bolus doses for maintenance of muscle relaxation

Serious adverse events	Zemuron Continuous Infusion Maintenance	Zemuron Bolus Maintenance	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 73 (0.00%)	1 / 64 (1.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
postoperative wound infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Zemuron Continuous Infusion Maintenance	Zemuron Bolus Maintenance	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 73 (12.33%)	10 / 64 (15.63%)	
Injury, poisoning and procedural complications			

procedural pain subjects affected / exposed occurrences (all)	9 / 73 (12.33%) 9	10 / 64 (15.63%) 12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2004	Amendment 01: Primary reason for amendment was to add a secondary objective, revise trial assessments to include electrocardiograms (ECGs), revise clinical trial design and statistical methods to comply with United States Food and Drug Administration (US FDA) Pediatric Written Request (PWR) and revise the exclusion criteria.
27 September 2004	Amendment 02: Primary reason for amendment was to revise the hazards and precautions section to include indications and possible complications of rapid sequence intubation.
27 September 2004	Amendment 03: Primary reason for amendment was to revise the exclusion criteria, standardize start time of administration of the intubating dose of Zemuron, and standardize reporting of fraction of inspired oxygen (FiO2).
27 September 2004	Amendment 04: Primary reason for amendment was to revise demographic data collected to comply with US FDA directive regarding collection of race and ethnicity data in clinical trials.
20 January 2005	Amendment 08: Primary reason for amendment was to indicate that non-US sites would not be conducting the trial under the US Investigational New Drug (IND) authorization and specify criteria for vital signs and ECG findings that are considered to be adverse events.
09 August 2005	Amendment 05: Primary reason for amendment was to exclude use of intravenous lidocaine and glycopyrrolate, define use of fentanyl for induction/maintenance of anesthesia, redefine the age groups for study participants, permit direct measurements of ventilatory parameters, include measurement of central body temperature, revise directions for induction with sevoflurane and description of boundary conditions for arterial oxygen percent saturation (SAO2) and end-tidal carbon dioxide (ETCO2), clarify description of reduction of sevoflurane after intubation and revise the blood sampling schedules.
15 September 2005	Amendment 06: Primary reason for amendment was to include reporting of Medical Device Reporting (MDR) reportable events.
09 December 2005	Amendment 07: Primary reason for amendment was to define use of local anesthetics for premedication and during surgery, define duration of induction of anesthesia, revise directions for administration of Zemuron for intubation, revise directions for measuring ventilatory parameters, revise the description of boundary conditions for SAO2 and include a requirement for obtaining acceptable practice neuromuscular recordings before neuromuscular transmission evaluation.
28 September 2006	Amendment 09: Primary reason for amendment was to indicate that sites from Argentina were to be involved in the clinical trial and add the use of epidural/caudal anesthesia to general anesthesia.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

15 July 2005	The P05797 protocol was performed under an FDA PWR. The protocol was amended several times in response to PWR amendments, FDA's comments on the protocol, changing FDA directives regarding the collection of data in clinical trials (e.g., FDA directive for collecting ethnicity data) or in response to requests from the trial site Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs). The major revisions to the protocol introduced in Protocol Amendments 5, 6 and 7 substantially altered trial conditions and assessment parameters. The trial was temporarily suspended during this period, and re-initiated after Protocol Amendment 8.	15 March 2006

Notes:

Limitations and caveats

None reported