Clinical trial results:
Intravenous Granisetron (Kytril) in the Prevention of Post-operative Nausea and Vomiting (PONV) in Pediatric Subjects Undergoing Tonsillectomy or Adenotonsillectomy

Summary

EudraCT number	2016-003260-39
Trial protocol	Outside EU/EEA
Global end of trial date	20 December 2007

Results information

Result version number	v1 (current)
This version publication date	15 July 2017
First version publication date	15 July 2017

Trial information

Trial identification

Sponsor protocol code	ML16633

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00231478
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	03 June 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effectiveness of two dose levels of intravenous (IV) granisetron (20 and 40 micrograms per kilogram [mcg/kg]) in preventing PONV, defined as total control (i.e., no nausea, no vomiting, no use of rescue medication) during the 2-hour interval following the time of extubation (end of surgery) in children aged 2 to 16 years.

Protection of trial subjects:

The study was conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study was fully adhere to the principles outlined in "guideline for Good Clinical Practice" of International Conference on Harmonisation (ICH) Tripartite Guideline (January 1997) or with local law if it afforded greater protection for the participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 2007
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	United States: 157
Worldwide total number of subjects	157
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	145
Adolescents (12-17 years)	12
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 171 pediatric participants undergoing elective tonsillectomy or adenotonsillectomy were randomized, 8 participants in the granisetron 20 mcg/kg dose group and and 6 participants in the 40 mcg/kg dose group did not receive study medication. Results are reported for 157 treated participants only.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Granisetron 20 mcg/kg

Arm description:

Granisetron, 20 mcg/kg IV injection 15 minutes prior to end of surgery on Day 1.

Arm type	Experimental
Investigational medicinal product name	Granisetron
Investigational medicinal product code	
Other name	Kytril
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 30-second IV injection of granisetron solution.

Arm title	Granisetron 40 mcg/kg

Arm description:

Granisetron, 40 mcg/kg IV injection 15 minutes prior to end of surgery on Day 1.

Arm type	Experimental
Investigational medicinal product name	Granisetron
Investigational medicinal product code	
Other name	Kytril
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single 30-second IV injection of granisetron solution.

Number of subjects in period 1	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg
Started	79	78
Completed	77	78
Not completed	2	0
Administrative	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Granisetron 20 mcg/kg
Reporting group description:	
Granisetron, 20 mcg/kg IV injection 15 minutes prior to end of surgery on Day 1.	
Reporting group title	Granisetron 40 mcg/kg
Reporting group description:	
Granisetron, 40 mcg/kg IV injection 15 minutes prior to end of surgery on Day 1.	

Reporting group values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg	Total
Number of subjects	79	78	157
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	5.96203	6.23077	
standard deviation	± 3.2441	± 3.09555	-
Gender Categorical Units: Subjects			
Female	25	45	70
Male	54	33	87

End points

End points reporting groups

Reporting group title	Granisetron 20 mcg/kg
Reporting group description:	
Granisetron, 20 mcg/kg IV injection 15 minutes prior to end of surgery on Day 1.	
Reporting group title	Granisetron 40 mcg/kg
Reporting group description:	
Granisetron, 40 mcg/kg IV injection 15 minutes prior to end of surgery on Day 1.	

Primary: Percentage of Participants With Total Control of PONV Over the 2 hours Following Extubation

End point title	Percentage of Participants With Total Control of PONV Over the 2 hours Following Extubation[1]
End point description:	
Percentage of participants with total control of PONV was defined as having no vomiting, no nausea, and no use of rescue medication after surgery. Evaluable population included all randomized participants who received their single dose of study treatment and had a postdose assessment of nausea, vomiting, or use of rescue medication in the 24 hours following extubation.	
End point type	Primary
End point timeframe:	
0-2 hours following extubation (end of surgery) on Day 1	
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: There was no formal hypothesis for this exploratory trial.	

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	85.7 (75 to 93)	90.4 (81 to 96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Total Control of PONV Over the 24 hours Following Extubation

End point title	Percentage of Participants With Total Control of PONV Over the 24 hours Following Extubation
End point description:	
Percentage of participants with total control was defined as no vomiting, no nausea, and no use of rescue medication after surgery. Evaluable population.	
End point type	Secondary

End point timeframe:

0-24 hours following extubation (end of surgery) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	65.7 (53 to 77)	61.6 (50 to 73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With No Vomiting Over the 2 hours Following Extubation

End point title	Percentage of Participants With No Vomiting Over the 2 hours Following Extubation

End point description:

Percentage of participants with no vomiting is described as no emesis up to 2 hours after surgery.
Evaluable population.

End point type	Secondary

End point timeframe:

0-2 hours following extubation (end of surgery) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	87.1 (77 to 94)	94.5 (87 to 98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With No Vomiting From the Time of Extubation Until Postanesthesia Care Unit (PACU) Discharge

End point title	Percentage of Participants With No Vomiting From the Time of Extubation Until Postanesthesia Care Unit (PACU) Discharge

End point description:

Any occurrence from the the time of extubation to PACU discharge were to be recorded at the PACU discharge assessment along with the time of PACU discharge.
Evaluable population.

End point type	Secondary

End point timeframe:

0 hour following extubation (end of surgery) up to PACU discharge (up to 24 hours) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	91.4 (82 to 97)	95.9 (88 to 99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With No Vomiting Over the 24 hours Following Extubation

End point title	Percentage of Participants With No Vomiting Over the 24 hours Following Extubation

End point description:

Percentage of participants with no vomiting is described as no emesis up to 24 hours after surgery. Evaluable population.

End point type	Secondary

End point timeframe:

0-24 hours following extubation (end of surgery) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	70 (58 to 80)	68.5 (57 to 79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Vomiting Episode

End point title	Time to First Vomiting Episode

End point description:

Time to first vomiting is described as the first event of emesis in hours. Participants not having a vomiting episode were censored at the total length of time (in hours) between the time of extubation and time of the 24 hour follow-up. Mean and standard error were estimated using Kaplan-Meier Survival

Analysis.
Evaluable population.

End point type	Secondary

End point timeframe:

0-24 hours following extubation (end of surgery) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: hours				
arithmetic mean (standard error)	18 (± 1.17)	17.8 (± 1.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With No Complaints of Nausea Over the 2 hours Following Extubation

End point title	Percentage of Participants With No Complaints of Nausea Over the 2 hours Following Extubation

End point description:

Percentage of participants with no complaints of nausea up to 2 hours after surgery were reported.
Evaluable population.

End point type	Secondary

End point timeframe:

0-2 hours following extubation (end of surgery) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	88.6 (79 to 95)	94.5 (87 to 98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With No Complaints of Nausea From the Time of Extubation Until PACU Discharge

End point title	Percentage of Participants With No Complaints of Nausea From the Time of Extubation Until PACU Discharge

End point description:

Any occurrence of nausea from the time of extubation until PACU discharge were to be recorded at the PACU discharge assessment along with the time of PACU discharge.
Evaluable population.

End point type	Secondary

End point timeframe:

0 hour following extubation (end of surgery) up to PACU discharge (up to 24 hours) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	91.4 (82 to 97)	97.3 (90 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With No Complaints of Nausea Over the 24 hours Following Extubation

End point title	Percentage of Participants With No Complaints of Nausea Over the 24 hours Following Extubation

End point description:

Percentage of participants with no complaints of nausea over 24 hours following the extubation were reported.
Evaluable population.

End point type	Secondary

End point timeframe:

0-24 hours following extubation (end of surgery) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	80 (69 to 89)	84.9 (75 to 92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With No Rescue Medication Use

End point title	Percentage of Participants With No Rescue Medication Use

End point description:

Percentage of participants who did not require rescue medication from extubation until PACU discharge were reported.
Evaluable population.

End point type	Secondary

End point timeframe:

0 hour following extubation (end of surgery) up to PACU discharge (up to 24 hours) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: percentage of participants				
number (confidence interval 95%)	94.2 (86 to 98)	97.2 (90 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Use of Rescue Medication

End point title	Time to First Use of Rescue Medication

End point description:

Any rescue medication used from the time of extubation up to 24 hours after extubation were to be recorded. If a rescue medication does not have any time indication, the time was set to equal the time of the earliest nausea episode or vomiting episode prior to discharge from the PACU. If a rescue medication does not have any time indication and no nausea or vomiting episodes are reported, the time of first rescue medication use was imputed as 1 minute following the time of extubation.
Participants not using rescue medication were censored at the total length of time (in hours) between the time of extubation and time of discharge from the PACU. Mean and standard error were estimated using Kaplan-Meier Survival Analysis.
Evaluable population.

End point type	Secondary

End point timeframe:

0-24 hours following extubation (end of surgery) on Day 1

End point values	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	73		
Units: hours				
arithmetic mean (standard error)	3.9 (± 0.12)	8.7 (± 0.35)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to 16 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups	
Reporting group title	Granisetron 20 mcg/kg
Reporting group description: Granisetron, 20 mcg/kg IV injection 15 minutes prior to end of surgery on Day 1.	
Reporting group title	Granisetron 40 mcg/kg
Reporting group description: Granisetron, 40 mcg/kg IV injection 15 minutes prior to end of surgery on Day 1.	

Serious adverse events	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 79 (7.59%)	2 / 78 (2.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	2 / 79 (2.53%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Migraine			
subjects affected / exposed	1 / 79 (1.27%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Tonsillar haemorrhage			
subjects affected / exposed	1 / 79 (1.27%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 79 (2.53%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral intake reduced			
subjects affected / exposed	1 / 79 (1.27%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	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	Granisetron 20 mcg/kg	Granisetron 40 mcg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 79 (7.59%)	4 / 78 (5.13%)	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 79 (7.59%)	4 / 78 (5.13%)	
occurrences (all)	6	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2007	Amendment 1: The primary and secondary objective and endpoint was clarified as the proportion of study participants with total control over the 2 and 24 hours following extubation, respectively. Secondary objectives and endpoints regarding the proportion of study participants who required granisetron 10 mcg/kg rescue due to prophylaxis failure and the response to granisetron rescue therapy were removed, secondary endpoints regarding the use of rescue medication no longer specified that rescue medication was granisetron 10 mcg/kg. Procedures regarding the use of rescue treatment were changed so as to specify that with the exception of 5-HT3 antagonists (prohibited). Additional secondary endpoints (proportions of study participants with vomiting and with/without complaints of nausea over different time periods) were provided to better support the secondary objective regarding the effectiveness of the two dose levels of granisetron. The exploratory objectives and endpoints regarding QT intervals and Chem-21 laboratory assessments were added. The maximum allowable granisetron dose of 3 milligrams (mg) was removed.
08 May 2007	Amendment 2: The intraoperative and post-operative dose of IV hydromorphone to be given as PACU analgesia was corrected (from 0.05 milligrams per kilogram [mg/kg] with a maximum dose of 1 mg to 0.005 mg/kg [no maximum dose provided]).
02 July 2007	Amendment 3: Clarified that intraoperative neuromuscular blockade was optional and that study participants who received it would also receive a neuromuscular blockade reversal agent.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: