



## Clinical trial results:

### A Multicenter, Double-blind, Double-dummy, Randomized, Parallel Group, Stratified Study to Evaluate the Efficacy and Safety of a Single IV Dose of Palonosetron Compared to a Single IV Dose of Ondansetron to Prevent Postoperative Nausea and Vomiting in Pediatric Patients

#### Summary

EudraCT number	2010-022971-79
Trial protocol	CZ PL HU
Global end of trial date	27 March 2012

#### Results information

Result version number	v1 (current)
This version publication date	17 April 2016
First version publication date	17 April 2016

#### Trial information

##### Trial identification

Sponsor protocol code	PALO-10-14
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01395901
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Helsinn Healthcare SA
Sponsor organisation address	Via Pian Scairolo 9, Lugano/Pazzallo, Switzerland, 6912
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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?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 September 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 March 2012
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Main objectives of the trial:

- The primary objective of this study is to evaluate the efficacy of a single palonosetron intravenous (IV) dose compared to a single ondansetron IV dose in the prevention of postoperative nausea and vomiting (PONV) through 24 hours after surgery in children aged from neonates up to less than 17 years undergoing elective surgical procedures requiring general intravenous anesthesia.

Protection of trial subjects:

For all patients, written informed consent signed by the parent(s)/legal guardian(s) was obtained prior to enrollment. For patients of appropriate age and intellectual maturity, the signed assent form was obtained in compliance with local laws and regulations.

Background therapy:

NA

Evidence for comparator:

Ondansetron (Zofran®) was selected as the active comparator since this drug is considered to be the current standard of care in the US for the prevention of PONV in pediatric surgical patients.

Actual start date of recruitment	14 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Hungary: 221
Country: Number of subjects enrolled	United States: 166
Country: Number of subjects enrolled	Russian Federation: 71
Country: Number of subjects enrolled	Ukraine: 125
Country: Number of subjects enrolled	Argentina: 13
Worldwide total number of subjects	670
EEA total number of subjects	295

Notes:

### Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	47
Children (2-11 years)	487
Adolescents (12-17 years)	136
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 44 sites were initiated in seven countries with 12, 9, 5, 5, 5, 6 and 2 investigative sites in the United States, Ukraine, Hungary, Poland, Russia, Czech Republic and Argentina. Patients were enrolled into the study by 39 out of 44 Investigators enrolling at least one patient.

### Pre-assignment

Screening details:

Out of total 670 randomised patients, 9 patients (5 in Palonosetron and Placebo to Ondansetron group and 4 in Ondansetron and Placebo to Palonosetron group), did not receive the study drug and hence were not included in the Full Analysis Set (FAS) population.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Palonosetron and Placebo to Ondansetron

Arm description:

Intervention: Drug: Palonosetron

Palonosetron: Single dose Palonosetron IV 1 mcg/kg (up to a maximum total dose of 0.075 mg)

Placebo to Ondansetron

Arm type	Experimental
Investigational medicinal product name	Palonosetron
Investigational medicinal product code	NA
Other name	Aloxi
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single dose Palonosetron IV 1 mcg/kg (up to a maximum total dose of 0.075 mg).

Investigational medicinal product name	Placebo to Ondansetron
Investigational medicinal product code	NA
Other name	NA
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single dose matching placebo IV.

<b>Arm title</b>	Ondansetron and Placebo to Palonosetron
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Arm description:

Intervention: Drug: Comparator: Ondansetron

Ondansetron: Single dose Ondansetron IV:

0 months to 12 years dose: 0.1 mg/kg for  $\leq 40$  kg and 4 mg for  $>40$  kg;

13 years to less than 17 years dose: 4 mg

Placebo to Palonosetron

Arm type	Active comparator
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Investigational medicinal product name	Ondansetron
Investigational medicinal product code	NA
Other name	Zofran
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single dose Ondansetron IV:

0 months to 12 years dose: 0.1 mg/kg for  $\leq 40$  kg and 4 mg for  $>40$  kg;

13 years to less than 17 years dose: 4 mg.

Investigational medicinal product name	Placebo to Palonosetron
Investigational medicinal product code	NA
Other name	NA
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single dose matching placebo IV.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron
Started	331	330
Completed	326	329
Not completed	5	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	1
Lost to follow-up	4	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of total 670 randomised patients, 9 patients (5 in Palonosetron and Placebo to Ondansetron group and 4 in Ondansetron and Placebo to Palonosetron group), did not receive the study drug and hence were not included in the Full Analysis Set (FAS) population.

## Baseline characteristics

### Reporting groups

Reporting group title	Palonosetron and Placebo to Ondansetron
Reporting group description:	
Intervention: Drug: Palonosetron	
Palonosetron: Single dose Palonosetron IV 1 mcg/kg (up to a maximum total dose of 0.075 mg)	
Placebo to Ondansetron	
Reporting group title	Ondansetron and Placebo to Palonosetron
Reporting group description:	
Intervention: Drug: Comparator: Ondansetron	
Ondansetron: Single dose Ondansetron IV:	
0 months to 12 years dose: 0.1 mg/kg for ≤ 40 kg and 4 mg for >40 kg;	
13 years to less than 17 years dose: 4 mg	
Placebo to Palonosetron	

Reporting group values	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron	Total
Number of subjects	331	330	661
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	7.82	7.43	
standard deviation	± 4.44	± 4.32	-
Gender categorical			
Units: Subjects			
Female	132	129	261
Male	199	201	400
Age customized			
Units: Subjects			
<2 years	22	24	46
2 <6 years	124	123	247
6 <12 years	117	117	234
12 <17 years	68	66	134
Ethnicity			
Units: Subjects			
Hispanic or Latino	24	21	45
Not Hispanic or Latino	307	309	616

Race			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	1	1	2
Black or African American	13	12	25
White	315	312	627
More than one race	0	1	1
Unknown or Not Reported	2	3	5

## End points

### End points reporting groups

Reporting group title	Palonosetron and Placebo to Ondansetron
Reporting group description:	
Intervention: Drug: Palonosetron	
Palonosetron: Single dose Palonosetron IV 1 mcg/kg (up to a maximum total dose of 0.075 mg)	
Placebo to Ondansetron	
Reporting group title	Ondansetron and Placebo to Palonosetron
Reporting group description:	
Intervention: Drug: Comparator: Ondansetron	
Ondansetron: Single dose Ondansetron IV:	
0 months to 12 years dose: 0.1 mg/kg for $\leq 40$ kg and 4 mg for $>40$ kg;	
13 years to less than 17 years dose: 4 mg	
Placebo to Palonosetron	

### Primary: Proportion of Patients With Complete Response

End point title	Proportion of Patients With Complete Response
End point description:	
Complete Response was defined as no vomiting, no retching, and no use of antiemetic rescue medication during the first 24 hours postoperatively, starting at T0. Time 0 (T0) was defined as the time when the patient wakes up and is able to show any active reaction postoperatively. The Full Analysis Set (FAS) included all randomized patients who received the active study drug, general anesthesia and surgery (evaluable patients). Following the intent-to-treat principle, patients were assigned to the study treatment arm according to their randomized treatment.	
End point type	Primary
End point timeframe:	
0-24 hours after T0	

End point values	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	330		
Units: percentage of patients				
number (confidence interval 95%)	78.2 (73.3 to 82.5)	82.7 (78.1 to 86.6)		

### Statistical analyses

Statistical analysis title	Comparison of Proportion of Patients With Complete
Statistical analysis description:	
The null hypothesis (H0) was stated as:	
• H0 : CR 0-24 hr palonosetron - CR 0-24 hr ondansetron $<-10\%$	
The alternative hypothesis (H1) was stated as:	
• H1 : CR 0-24 hr palonosetron - CR 0-24 hr ondansetron $>-10\%$	
A power of 80% was used for sample size computation.	
Comparison groups	Palonosetron and Placebo to Ondansetron v Ondansetron and



	Placebo to Palonosetron
Number of subjects included in analysis	661
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	1.7

Notes:

[1] - For the primary efficacy analysis, the confidence interval (CI) was built on the FAS using the stratum adjusted Mantel-Haenszel (MH) method with correction of continuity. The non-inferiority margin was -10%.

### Secondary: Proportion of Patients With no Vomiting

End point title	Proportion of Patients With no Vomiting
End point description:	
Time 0 (T0) was defined as the time when the patient wakes up and is able to show any active reaction postoperatively. The Full Analysis Set (FAS) population.	
End point type	Secondary
End point timeframe:	
0-24 hours after T0	

End point values	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	330		
Units: percentage of patients				
number (confidence interval 95%)	83.1 (78.5 to 86.9)	87.6 (83.4 to 90.8)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Patients Without Emetic Episodes

End point title	Proportion of Patients Without Emetic Episodes
End point description:	
An emetic episode was defined as one or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Time 0 (T0) was defined as the time when the patient wakes up and is able to show any active reaction postoperatively. The Full Analysis Set (FAS) population.	
End point type	Secondary
End point timeframe:	
0-24 hours after T0	

End point values	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	330		
Units: percentage of patients				
number (confidence interval 95%)	80.1 (75.3 to 84.1)	83.9 (79.4 to 87.6)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Patients Without Antiemetic Rescue Medication

End point title	Proportion of Patients Without Antiemetic Rescue Medication
End point description:	
Rescue medications are any medications with potential antiemetic effect taken in the 24 hours after patient wake-up from anesthesia (T0). Time 0 (T0) was defined as the time when the patient wakes up and is able to show any active reaction postoperatively. The Full Analysis Set (FAS) population.	
End point type	Secondary
End point timeframe:	
0-24 hours after T0	

End point values	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	330		
Units: percentage of patients				
number (confidence interval 95%)	93.1 (89.6 to 95.4)	96.4 (93.6 to 98)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Patients Without Nausea (Patient Aged > 6 Years)

End point title	Proportion of Patients Without Nausea (Patient Aged > 6 Years)
End point description:	
Included patients in the Full Analysis Set (FAS) population who were aged $\geq 6$ years.	
End point type	Secondary

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End point timeframe:

0-24 hours after T0

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<b>End point values</b>	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	183		
Units: percentage of patients				
number (confidence interval 95%)	83.2 (76.9 to 88.2)	82 (75.5 to 87.1)		

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 30 days post treatment

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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### Reporting groups

Reporting group title	Palonosetron and Placebo to Ondansetron
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Reporting group description:

Intervention: Drug: Palonosetron

Palonosetron: Single dose Palonosetron IV 1 mcg/kg (up to a maximum total dose of 0.075 mg)

Placebo to Ondansetron

Reporting group title	Ondansetron and Placebo to Palonosetron
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Reporting group description:

Intervention: Drug: Comparator: Ondansetron

Ondansetron: Single dose Ondansetron IV:

0 months to 12 years dose: 0.1 mg/kg for  $\leq 40$  kg and 4 mg for  $>40$  kg;

13 years to less than 17 years dose: 4 mg

Placebo to Palonosetron

Serious adverse events	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 331 (1.21%)	11 / 330 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioma			
subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
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	1 / 331 (0.30%)	5 / 330 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric anastomosis complication			

subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 330 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 331 (0.30%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 331 (0.30%)	0 / 330 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	1 / 331 (0.30%)	0 / 330 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 331 (0.30%)	0 / 330 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palatal oedema			
subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 331 (0.30%)	0 / 330 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 331 (0.30%)	0 / 330 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulpitis dental			
subjects affected / exposed	1 / 331 (0.30%)	0 / 330 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 331 (0.30%)	0 / 330 (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	1 / 331 (0.30%)	2 / 330 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 331 (0.00%)	1 / 330 (0.30%)	
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: 2 %

<b>Non-serious adverse events</b>	Palonosetron and Placebo to Ondansetron	Ondansetron and Placebo to Palonosetron	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	212 / 331 (64.05%)	203 / 330 (61.52%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	147 / 331 (44.41%)	123 / 330 (37.27%)	
occurrences (all)	149	126	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 331 (1.21%)	10 / 330 (3.03%)	
occurrences (all)	4	10	
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	2 / 331 (0.60%)	12 / 330 (3.64%)	
occurrences (all)	2	19	
Pain			
subjects affected / exposed	15 / 331 (4.53%)	15 / 330 (4.55%)	
occurrences (all)	16	16	
Pyrexia			
subjects affected / exposed	22 / 331 (6.65%)	25 / 330 (7.58%)	
occurrences (all)	22	30	
Ear and labyrinth disorders			

Ear pain subjects affected / exposed occurrences (all)	6 / 331 (1.81%) 6	9 / 330 (2.73%) 9	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 331 (0.60%) 2	8 / 330 (2.42%) 8	
Vomiting subjects affected / exposed occurrences (all)	5 / 331 (1.51%) 5	10 / 330 (3.03%) 12	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	7 / 331 (2.11%) 7	5 / 330 (1.52%) 5	
Oropharyngeal pain subjects affected / exposed occurrences (all)	27 / 331 (8.16%) 28	37 / 330 (11.21%) 39	
Skin and subcutaneous tissue disorders Scar subjects affected / exposed occurrences (all)	7 / 331 (2.11%) 7	4 / 330 (1.21%) 4	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

Enrollment of non-white or Hispanic patients was low and limited assessment of any potential impact of these demographic characteristics.
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Notes: