Clinical trial results:
A multicenter, multinational, randomized, double-blind, pharmacokinetic and pharmacodynamic (PK/PD) dose-finding study of oral netupitant administered concomitantly with oral palonosetron in pediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

Summary

EudraCT number	2020-003730-20
Trial protocol	Outside EU/EEA
Global end of trial date	30 September 2019

Results information

Result version number	v1 (current)
This version publication date	26 December 2020
First version publication date	26 December 2020

Trial information

Trial identification

Sponsor protocol code	NEPA-15-31

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03204279
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Helsinn Healthcare SA
Sponsor organisation address	Via di Pian Scairolo , Lugano, Switzerland, 6912
Public contact	Paolo Villasanta, Helsinn Healthcare SA, paolo.villasanta@helsinn.com
Scientific contact	Paolo Villasanta, Helsinn Healthcare SA, paolo.villasanta@helsinn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001198-PIP03-17
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	30 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PK/PD correlation between netupitant exposure and antiemetic efficacy after a single oral netupitant administration, concomitantly with oral palonosetron in pediatric cancer patients receiving chemotherapy

Protection of trial subjects:

The study was conducted in full compliance with the principles outlined in the Declaration of Helsinki the International Council on Harmonisation (ICH) guidelines [2], as well as all local laws, regulations, and applicable guidelines of the countries in which the study was conducted.
The appropriateness of the clinical trial protocol as well as the risks and benefits to study participants were approved by relevant IRBs/IECs.
The study meets the ethical requirement in accordance with Article 8(1b) of Directive 2001/83/EC

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2017
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	Russian Federation: 14
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	Ukraine: 34
Worldwide total number of subjects	67
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)	23
Children (2-11 years)	28
Adolescents (12-17 years)	16

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 12 study sites were active for patient recruitment in Russia (3 sites), Serbia (2 sites), Ukraine (3 sites), and the United States (US) (4 sites). One site in the US screened a patient but he was not enrolled (screen failure). the study period was 22 months from 14 Sept 2017 to 16 Jul 2019

Pre-assignment

Screening details:

Randomization was used to avoid bias in assigning treatment to patients and to increase the likelihood that known and unknown patient attributes were evenly balanced across treatment groups. Randomization/treatment assignment of eligible patients was done using IWRS integrated with an Electronic Data Capture (EDC) system.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Netupitant 1.33 mg/kg plus Palonosetron

Arm description:

single oral dose of Netupitant 1.33 mg/kg up to a maximum of 100 mg (for patients < 3 months of age the netupitant dose will be 0.8 mg/kg) administered with single oral dose of 20 µg/Kg palonosetron up to a maximum of 1.5 mg

Arm type	Experimental
Investigational medicinal product name	netupitant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Netupitant 1.33mg/kg up to 100mg

Arm title	Netupitant 4 mg/kg Plus Palonosetron

Arm description:

Single oral dose of Netupitant 4mg/kg up to a maximum of 300 mg (for patients<3 months of age the netupitant will be 2.4 mg/kg) administered with single oral dose of 20µg/kg palonosetron up to a maximum of 1.5 mg

Arm type	Experimental
Investigational medicinal product name	netupitant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

netupitant 4 mg/kg oral suspension up to a maximum of 300 mg

Number of subjects in period 1	Netupitant 1.33 mg/kg plus Palonosetron	Netupitant 4 mg/kg Plus Palonosetron
Started	34	33
Completed	34	32
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Netupitant 1.33 mg/kg plus Palonosetron
Reporting group description:	
single oral dose of Netupitant 1.33 mg/kg up to a maximum of 100 mg (for patients < 3 months of age the netupitant dose will be 0.8 mg/kg) administered with single oral dose of 20 µg/Kg palonosetron up to a maximum of 1.5 mg	
Reporting group title	Netupitant 4 mg/kg Plus Palonosetron
Reporting group description:	
Single oral dose of Netupitant 4mg/kg up to a maximum of 300 mg (for patients<3 months of age the netupitant will be 2.4 mg/kg) administered with single oral dose of 20µg/kg palonosetron up to a maximum of 1.5 mg	

Reporting group values	Netupitant 1.33 mg/kg plus Palonosetron	Netupitant 4 mg/kg Plus Palonosetron	Total
Number of subjects	34	33	67
Age categorical			
Units: Subjects			
patients 1 months to 3 months of age	1	0	1
patients 3 month to 6 months of age	3	2	5
patients 6 months to 1 year of age	4	5	9
patients 1 year to 2 years	3	5	8
patients 2 years to 5 years	6	6	12
patients 5 years to 12 years	8	8	16
patients 12 years to 18 years	9	7	16
Age continuous			
Units: months			
arithmetic mean	6.6	5.6	
standard deviation	± 6.29	± 5.46	-
Gender categorical			
Units: Subjects			
Female	13	14	27
Male	21	19	40
age			
Units: Subjects			
patients 1 month to 3 months	1	0	1
patients 3 month to 6 months of age	3	2	5
patients 6 months to 1 year of age	4	5	9
patients 2 years to 5 years	6	6	12
patients 5 years to 12 years	8	8	16
patients 12 years to 18 years	9	7	16
patients 1 to 2 years	3	5	8

End points

End points reporting groups

Reporting group title	Netupitant 1.33 mg/kg plus Palonosetron
Reporting group description:	
single oral dose of Netupitant 1.33 mg/kg up to a maximum of 100 mg (for patients < 3 months of age the netupitant dose will be 0.8 mg/kg) administered with single oral dose of 20 µg/Kg palonosetron up to a maximum of 1.5 mg	
Reporting group title	Netupitant 4 mg/kg Plus Palonosetron
Reporting group description:	
Single oral dose of Netupitant 4mg/kg up to a maximum of 300 mg (for patients<3 months of age the netupitant will be 2.4 mg/kg) administered with single oral dose of 20µg/kg palonosetron up to a maximum of 1.5 mg	

Primary: Area Under the Plasma Concentration Versus Time Curve From Time Zero to Infinity (AUC0-inf) of Netupitant

End point title	Area Under the Plasma Concentration Versus Time Curve From Time Zero to Infinity (AUC0-inf) of Netupitant[1]
End point description:	
Mean values of area under the plasma Concentration versus time curve from time zero to infinity (AUC0-inf) of netupitant after a single oral netupitant administration, concomitantly with oral palonosetron, in pediatric cancer patients receiving HEC or MEC cycles. AUC estimates are obtained by non-compartmental analysis of population modelpredicted individual plasma concentration-time profiles.	
End point type	Primary
End point timeframe:	
within 168 hours after netupitant administration. A sampling windows approach will be used by collecting a single blood sample from each patient in one of these time windows: from 2 to 8 h, from 24 to 48 h, from 72 to 96 h and from 120 to 168 h	

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: individual pk parameters were calculated for each arms and descriptive statistics are presented

End point values	Netupitant 1.33 mg/kg plus Palonosetron	Netupitant 4 mg/kg Plus Palonosetron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: AUC				
geometric mean (geometric coefficient of variation)				
patients 6 months to 1 year of age	7637 (± 113)	8617 (± 45.2)		
patients 1 month to 3 months of age	4460 (± 0)	0 (± 0)		
patients 3 months to 6 months	3849 (± 91.3)	17340 (± 36.4)		
patients 1 year to 2 years	2276 (± 29.8)	9886 (± 59.6)		
patients 2 years to 5 years	3135 (± 44.0)	14404 (± 131)		
patients 5 years to 12 years	2676 (± 29.8)	10154 (± 70.7)		
patients 12 years to 18 years	3107 (± 54.9)	12266 (± 26.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) of Netupitant

End point title	Maximum Plasma Concentration (Cmax) of Netupitant[2]

End point description:

End point type	Primary

End point timeframe:

A sampling window approach was used by collecting a single blood sample from each patient in one of these time windows: from 2 to 8h, from 24h to 48h, from 72h to 96h and from 120 to 168h

Notes:

[2] - 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: individual pk parameters were calculated for each arms and descriptive statistics are presented

End point values	Netupitant 1.33 mg/kg plus Palonosetron	Netupitant 4 mg/kg Plus Palonosetron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: Cmax				
geometric mean (geometric coefficient of variation)				
patient 1 month to 3 months	60.8 (± 0)	0 (± 0)		
patient 3 months to 6 months	76.0 (± 27.1)	233 (± 4.25)		
patients to 6 months to 12 months	133 (± 71.7)	255 (± 31.2)		
patients 1 year to 2 years	69.5 (± 19.3)	275 (± 38.2)		
patients 2 years to 5 years	74.0 (± 32.3)	266 (± 55.0)		
patients 5 years to 12 years	67.9 (± 32.3)	213 (± 20.1)		
patients 12 years to 18 years	76.8 (± 27.3)	274 (± 15.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: percentage of pediatric patients with complete response during the delayed phase

End point title	percentage of pediatric patients with complete response during the delayed phase

End point description:

percentage of pediatric patients with complete response (CR, i.e., no emetic episodes and no rescue medication) during the delayed phase (>24 to 120 h after the start of chemotherapy on day 1) after a

single oral netupitant administration, concomitantly with oral palonosetron, in pediatric cancer patients receiving HEC or MEC cycles
The number and percentage of patients with CR (i.e., no emetic episodes and no rescue medication) during the delayed (>24 to 120 hours), acute (0 to 24 hours), and overall (0 to 120 hours) phases after the start of chemotherapy administration on Day 1, along with the 95% confidence intervals (CIs), are calculated using the Clopper-Pearson (exact) method and are summarized by treatment group, overall, and strata for the FAS.

End point type	Secondary

End point timeframe:

24-120 hours after the start of chemotherapy day 1

End point values	Netupitant 1.33 mg/kg plus Palonosetron	Netupitant 4 mg/kg Plus Palonosetron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	31		
Units: percentage				
number (confidence interval 95%)	70.59 (52.5 to 84.9)	70.97 (52.0 to 85.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from the first dose of study drug on Visit 2 (day 1, inclusively) until Visit 5 (follow uo, day 14[+3]	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Netupitant 1.33 mg/kg plus Palonosetron
Reporting group description: -	
Reporting group title	Netupitant 4 mg/kg Plus Palonosetron
Reporting group description: -	

Serious adverse events	Netupitant 1.33 mg/kg plus Palonosetron	Netupitant 4 mg/kg Plus Palonosetron	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)	3 / 32 (9.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 34 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 34 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Netupitant 1.33 mg/kg plus Palonosetron	Netupitant 4 mg/kg Plus Palonosetron	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 34 (64.71%)	22 / 32 (68.75%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 34 (8.82%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
White blood cell count decreased			
subjects affected / exposed	2 / 34 (5.88%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 34 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 34 (2.94%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 34 (26.47%)	7 / 32 (21.88%)	
occurrences (all)	9	7	
Febrile neutropenia			
subjects affected / exposed	2 / 34 (5.88%)	3 / 32 (9.38%)	
occurrences (all)	2	3	
Leukopenia			

subjects affected / exposed	8 / 34 (23.53%)	4 / 32 (12.50%)	
occurrences (all)	8	4	
Neutropenia			
subjects affected / exposed	3 / 34 (8.82%)	6 / 32 (18.75%)	
occurrences (all)	3	6	
Thrombocytopenia			
subjects affected / exposed	10 / 34 (29.41%)	6 / 32 (18.75%)	
occurrences (all)	10	6	
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	1 / 34 (2.94%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 34 (2.94%)	5 / 32 (15.63%)	
occurrences (all)	1	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 34 (2.94%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Stomatitis			
subjects affected / exposed	2 / 34 (5.88%)	5 / 32 (15.63%)	
occurrences (all)	2	5	
Vomiting			
subjects affected / exposed	2 / 34 (5.88%)	3 / 32 (9.38%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			
hypoglycemia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 32 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2019	Following a specific recommendation from FDA, for purposes of facilitating enrollment in the study, enrollment of the age cohorts 3 < 6 months and 1 < 3 months and birth < 1 month is allowed in parallel (instead of sequentially), keeping the original treatment dose escalation scheme (i.e., first lowest doses are to be given in parallel in all remaining age cohorts, then highest doses are to be given in parallel in all the remaining age cohorts). This approach was also endorsed by DSMB members.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported