



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