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Pharmacokinetic investigation aimed to demonstrate that the new liquid formulation containing (fos)netupitant and palonosetron is similar to the lyophilized (freeze-dried) formulation

Submission date 11/12/2020	**Recruitment status** Stopped	[ ] Prospectively registered [ ] Protocol
Registration date 26/02/2021	**Overall study status** Stopped	[ ] Statistical analysis plan [ ] Results
Last Edited 25/10/2021	**Condition category** Cancer	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The medication under investigation is used in the common medical practice to prevent nausea and vomiting in patients under chemotherapy treatment. A new liquid formulation has been developed to be injected into the vein. In the first part of the present trial, the main aim is to verify the possibility of shortening the injection time period of the liquid formulation. In the second part of the study, the main aim is to demonstrate that the new formulation results in a medication exposure similar to the ones observed with the freeze-dried formulation.

Who can participate?
Healthy volunteers aged between 18 and 55 years old

What does the study involve?
The treatment being investigated (test treatment) is the combination fosnetupitant /palonosetron 235 mg/0.25 mg (IV NEPA FDCliq), which is given via a needle into the vein in a single dose. This treatment will be compared to the reference treatment of fosnetupitant /palonosetron 235 mg/0.25 mg (IV NEPA FDClyo), which is infused slowly into the vein.

In part A of the study, 24 participants will receive the treatment being investigated in order to investigate the possibility of shortening the injection duration.

In part B of the study, 40 participants will be randomly allocated to receive either test followed by reference treatment, or reference followed by test treatment.

In both parts of the study blood samples will be taken from participants at regular intervals.

What are the possible benefits and risks of participating?
No specific benefits for the healthy subjects participating in the current study are foreseen except for medical screening.

Previous studies in more than 400 male and female cancer patients have shown that the treatment being investigated is well-tolerated, similar to the reference treatment. Adverse reactions reported with the reference treatment in a small proportion of the participants were headache, constipation, and fatigue.

Where is the study run from?
The CROSS Research SA Phase 1 Unit (Switzerland)

When is the study starting and how long is it expected to run for?
From July 2019 to September 2020

Who is funding the study?
Helsinn Healthcare SA (Switzerland)

Who is the main contact?
Dr Tulla Spinelli, Tulla.Spinelli@helsinn.com

Contact information

Type(s)
Public

Contact name
Dr Tulla Spinelli

Contact details
Helsinn Healthcare SA
Via Pian Scairolo 9
Lugano
Switzerland
6912
+41 919852121
tulla.spinelli@helsinn.com

Type(s)
Scientific

Contact name
Dr Milko Radicioni

ORCID ID
https://orcid.org/0000-0002-3940-8375

Contact details
CROSS Research SA Phase I Unit
Via FA Giorgioli 14
Arzo

Switzerland
6864
+41 916300510
milko.radicioni@croalliance.com

Additional identifiers

Protocol serial number
Sponsor code: NEPA-19-13, CRO code: CRO-PK-19-339

Study information

Scientific Title
A phase I, open-label, single-dose study in male and female healthy subjects to assess the safety and pharmacokinetics of IV NEPA administered as IV bolus versus 30-minute IV infusion

Study objectives
The study will demonstrate that it is possible to shorten the injection duration of the liquid formulation without this affecting the exposure to the active principles as compared to the exposure obtained from 30 min IV administration of the lyophilised solution.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 05/11/2019, substantial amendment 1 approved 10/02/2020, Comitato Etico Cantonale (c/o Ufficio di sanità, Via Orico 5, 6501 Bellinzona, Switzerland; +41 91 814 30 57; dss-ce@ti.ch), ref: 3532, project ID: 2019-01997
2. Approved 16/01/2020, substantial amendment 1 approved 28/02/2020, The Federal Health Authorities (Swissmedic) (Swiss Agency for Therapeutic Products, Clinical trials, Hallerstrasse 7, 3012 Bern, Switzerland; +41 58 462 03 87; ct.medicinalproducts@swissmedic.ch), ref: 2020DR1011

Primary study design
Interventional

Study design
Two-part study: an observational study to determine injection duration and a phase I open-label, single-dose randomized cross over safety and pharmacokinetics study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chemotherapy-induced nausea and vomiting

Interventions
The study is divided into two parts (A and B). Part A is composed of 3 consecutive cohorts of 8 subjects each (fosnetupitant/palonosetron 235 mg/0.25 mg injectable solution, IV NEPA FDCliq, given over 15, 5, or 2 minutes). Then Part B included 40 subjects randomized in 2 arms

(fosnetupitant/palonosetron 235 mg/0.25 mg lyophilized powder (Akynzeo®), IV NEPA FDClyo, diluted in 50 ml given in 30 min vs Liquid given in either 15 or 5 or 2 minutes as resulting from part A) with a cross-over design. Part A is not randomized, the first 8 subjects are assigned to the first cohort. Part B is randomized 1:1, using a sealed envelope established on a pre-defined randomization list.

Part A:
3 consecutive cohorts of 8 subjects will receive a single IV dose of 20 ml of the liquid formulation corresponding to the fixed-dose combination fosnetupitant/palonosetron 235 mg/0.25 mg. In each cohort, the injection duration should vary as follows:
1. Cohort 1: 15 min
2. Cohort 2: 5 min
3. Cohort 3: either 2 or 10 min according to the outcome of Cohort 2
Predefined stopping rules will be considered for deciding about continuing with the next cohort and shorter injection duration. After cohort 1, if the injection duration of 15 min is found to be safe and well-tolerated, 5 min should be tested in cohort 2. After cohort 2, if the injection duration of 5 min is found to be safe and well-tolerated, 2 min should be tested in cohort 3. Otherwise, 10 min should be investigated.

Vital signs and ECGs will be measured pre-dose, and at 30 min, and 6 h after the injection

The PK samples will be collected immediately post-dose, between (2-5 or 10-15 min, on the basis of the treatment period), 20, 30, and 45 min, 1, 1.5, 2, 3, 4, 8, 12 and 24 h post-dose

In part A, the subject is followed up to 6 days from the study drug administration. At the end of each cohort, safety and tolerability results should be evaluated by the Investigator and the study Sponsor Medical Expert.

Study Part A will be stopped if any of the following criteria is met:
1. Any SAE experienced within 60 min after the end of the injection of the IMP by at least one subject in a cohort
2. Any AE coded with the same preferred term (PT) occurring to 2 subjects of the same cohort and both judged at least as possibly related to the IMP, of severe intensity and which occurs at the injection site
3. Any other AE coded with the same PT of severe intensity and experienced by 2 subjects of the same cohort within 60 min after the end of the injection of the IMP

Part B:
The selected safe shorter infusion duration resulting from part A will be applied in study part B. Two treatment periods are planned in Part B, with a wash-out period of at least 28 days between the treatment day of each period.

Vital signs and ECGs are measured at pre-dose, immediately post-dose, and 30 min, 6, and 24 h post-dose.

The PK samples will be collected pre-dose, 30 and 45 min, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168 and 192 h

In part B, the subject is followed up to 9 days from the study drug administration.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Fosnetupitant/palonosetron

Primary outcome(s)
Part A:
1. The shortest safe and tolerable duration of IV bolus injection of the liquid formulation assessed using the following:
1.1. Heart rate, electrical axes, and RR, PR, QRS, QT, QTcB, and QTcF intervals measured using electrocardiogram (ECG) at pre-dose, 30 min, and 6 h post-dose
1.2. Systolic blood pressure, diastolic blood pressure, and pulse rate measured using sphygmomanometer at pre-dose, 30 min, and 6 h post-dose
1.3. Adverse events measured from participant history up to 6 days post-dose

Part B:
1. Bioequivalence of the liquid formulation (at the injection duration defined in Part A) and the lyophilized formulation, estimated in terms of the extent of exposure to netupitant and palonosetron (area under the plasma drug concentration–time curve, AUC0-t), using a fully validated liquid chromatography with tandem mass spectrometry (LC-MSMS) at pre-dose, 30 and 45 min post-dose, and at 1, 1.5, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168 and 192 h post-dose

Key secondary outcome(s)
Part A:
1. Characterization of the pharmacokinetic (PK) profile in plasma of fosnetupitant, netupitant, and palonosetron using serum samples after injection of the liquid formulation measured immediately post-dose, between either 2-5 or 10-15 min (on the basis of the treatment period), 20, 30, and 45 min, 1, 1.5, 2, 3, 4, 8, 12 and 24 h post-dose

Part B:
1. Pharmacokinetic (PK) profile and kinetic parameters of netupitant and palonostren measured using fully validated liquid chromatography with tandem mass spectrometry (LC-MS-MS) at pre-dose, 30 and 45 min post-dose, and at 1, 1.5, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168 and 192 h post-dose
2. Safety and tolerability of the liquid formulation and the lyophilized formulation during the overall trial assessed using the following:
1.1. Heart rate, electrical axes, and RR, PR, QRS, QT, QTcB, and QTcF intervals measured using electrocardiogram (ECG) at pre-dose, immediately post-dose, 30 min, 6, and 24 h post-dose
1.2. Systolic blood pressure, diastolic blood pressure, and pulse rate measured using sphygmomanometer at pre-dose, immediately post-dose, 30 min, 6, and 24 h post-dose
1.3. Adverse events measured from participant history up to 9 days post-dose

Completion date
16/09/2020

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. Signed written informed consent before inclusion in the study
2. Aged 18 and 55 years
3. Body Mass Index (BMI) between 18.5 and 30 kg/m2
4. Vital signs, measured after 5 min at rest in the sitting position:
4.1. Systolic blood pressure between 100 and 139 mmHg
4.2. Diastolic blood pressure between 50 and 89 mmHg
4.3. Pulse rate between 50 and 90 bpm
5. Able to comprehend the full nature and purpose of the study, including possible risks and side effects, and able to co-operate with the Investigator and to comply with the requirements of the entire study
6. Women of child-bearing potential must have a negative pregnancy test result at screening and admission (Day -1) and be using at least one of the following reliable methods of contraception:
6.1. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
6.2. A non-hormonal intrauterine device [IUD] or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for ≥2 months before the screening visit
6.3. A male sexual partner who agrees to use a male condom with spermicide
6.4. A sterile sexual partner
7. Women of non-child-bearing potential or in post-menopausal status for ≥1 year

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
64

Key exclusion criteria
1. Electrocardiogram (ECG) 12-lead (supine position) with clinically significant abnormalities at screening
2. Clinically significant abnormal physical findings that could interfere with the objectives of the study
3. Clinically significant abnormal laboratory values at screening indicative of physical illness, or suggesting the subject’s exclusion is in their best interest
4. Ascertained or presumptive hypersensitivity to the active principles and/or formulations' ingredients, or history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study

5. Significant history, in the opinion of the Investigator, of renal, hepatic, gastrointestinal, cardiovascular (in particular history of superficial thrombophlebitis or deep vein thrombosis), respiratory, skin, hematological, endocrine, or neurological diseases that may interfere with the aim of the study
6. Taking medications, including over the counter (OTC) medications and herbal remedies, other than hormonal contraceptives for women in the 2 weeks before the first visit of the study
7. Use of an inducer or inhibitor of CYP3A4 enzymes (drugs, food, herbal remedies) in the 28 days (part A) or in the 7 days (part B) before the planned first study drug administration, and during the whole study period
8. Participation in the evaluation of any investigational product in the 3 months (calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first visit of the present study) before the first visit of this study
9. Blood donations or significant blood loss in the 3 months before the first visit of this study
10. History of drug, alcohol (>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2015-2020), caffeine (>5 cups coffee/tea/day), or tobacco abuse (≥10 cigarettes/day)
11. Positive result at the urine drug screening test at screening or Day -1
12. Positive alcohol breath test at Day -1
13. Vegetarian or abnormal diets (<1600 or >3500 kcal/day), or substantial changes in eating habits in the 4 weeks before screening
14. Pregnancy, breastfeeding, or positive or missing pregnancy test at screening or Day -1
15. Enrolment in a previous study of netupitant or fosnetupitant (alone or in combination with palonosetron)

Date of first enrolment
06/07/2020

Date of final enrolment
16/07/2020

Locations

Countries of recruitment
Switzerland

Study participating centre
CROSS Research SA, Phase 1 Unit
Via FA Giorgioli 14
Arzo
Switzerland
6864

Sponsor information

Organisation
Helsinn (Switzerland)

ROR
https://ror.org/01kdzkq48

Funder(s)

Funder type
Industry

Funder Name
Helsinn

Alternative Name(s)
Helsinn Group, Helsinn Holding, Helsinn Healthcare

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date