CROSS ALLIANCE
Contract Research Organisation for Scientific Services

HELSINN

CLINICAL STUDY PROTOCOL

Study CRO-PK-22-363 - Sponsor code PNET-22-08

A phase I, open label, single dose, two parts study in male and female healthy subjects to assess the safety and pharmacokinetics of Fosnetupitant 235 mg administered as IV bolus and of derived Netupitant and Netupitant metabolites

Sponsor: Helsinn Healthcare SA - Via Pian Scairolo 9,
CH-6912 Lugano - Switzerland
Phone: +41 91 985 21 21
Fax: +41 91 993 21 22

NCT number: NCT06840769

Document date: 24MAY2023

CLINICAL STUDY PROTOCOL

Study CRO-PK-22-363 - Sponsor code PNET-22-08

A phase I, open label, single dose, two parts study in male and female healthy subjects to assess the safety and pharmacokinetics of Fosnetupitant 235 mg administered as IV bolus and of derived Netupitant and Netupitant metabolites

Open label, single dose, two parts (part A and part B), safety and pharmacokinetics phase I study. Study Part B will be conducted according to a randomized cross-over design

Investigational product:	IV fosnetupitant 235 mg free base 20 mL ready to use solution for intravenous administration, Patheon Italia S.p.A., Italy
Reference product:	IV Akynzeo (235 mg fosnetupitant/0.25 mg palonosetron) in 20 mL injectable solution, Baxter Oncology GmbH, Germany
Placebo:	0.9% sodium chloride injection solution ready to use solution for intravenous administration (placebo), purchased from the market
Sponsor:	Helsinn Healthcare SA - Via Pian Scairolo 9, CH-6912 Lugano - Switzerland Phone: +41 91 985 21 21 Fax: +41 91 993 21 22
Investigator:	Milko Radicioni, MD - Principal Investigator CROSS Research S.A., Phase I Unit, Via F. A. Giorgioli 14 CH-6864 Arzo, Switzerland Phone: +41.91.64.04.450 Fax: +41.91.64.04.451 Email: clinic@croalliance.com
Development phase:	Phase I
Version and date:	CSP final version 3.0, 24MAY23

This study will be conducted in compliance with the protocol and the principles of Good Clinical Practice (GCP) [ICH topic E6 (R2)] and with the local regulatory requirements

This document comprises 99 pages

CLINICAL STUDY PROTOCOL AMENDMENT HISTORY

CSP version	Reason for change
Final version 3.0, 24MAY23	1) Protocol amendment implemented, as required by the competent Ethics Committee, in order to improve the check of safety and tolerability of the study treatment in study Part A, with particular attention to the planned infusion durations shorter than 30 min, i.e., planned cohorts 2, 3 and 4. Therefore, the 10 subjects of cohorts 2, 3 and 4, planned to test decreasing infusion durations of 15, 5 and 2 min, respectively, will be sequentially treated as subgroups of 3, 3 and 4 subjects. 2) Paragraph 18.3.4 "Reporting Serious Adverse Events" does not clearly define the reporting of SUSARs to Swissmedic (Competent Authority). As required by the Federal Health Authority, the paragraph is amended in accordance with ClinO, Art. 41. 3) Update of the bioanalytical laboratory denomination.

2 PROTOCOL APPROVAL

2.1 SPONSOR

Helsinn Healthcare SA

Medical Expert:

Study Coordinator:

Statistician:

Clinical Pharmacokineticist:

Drug Safety Specialist:

2.2 INVESTIGATOR

Study Title

A phase I, open label, single dose, two parts study in male and female healthy subjects to assess the safety and pharmacokinetics of Fosnetupitant 235 mg administered as IV bolus and of derived Netupitant and Netupitant metabolites

Study Number PNET-22-08

I have read and understood all pages of this clinical trial protocol and I agree that they contain all information required to conduct this trial. I agree to conduct the trial as outlined in the protocol and to comply with all terms and conditions set out therein. I confirm that I will conduct the trial in accordance with local regulations, ICH GCP "ICH Topic E6", R2, the provisions of the Declaration of Helsinki and with the Swiss Ordinance on Clinical Trials with the exception of Clinical Trials of Medical Devices 810.305 (ClinO) of 20 September 2013 (Status as of 26 May 2022) and all applicable regulatory requirements. I will keep strictly confidential any information pertaining to the study and/or regarding the Sponsor, using such information only to accomplish the present study tasks. I will direct, assist and oversee sub-Investigator(s) and other relevant staff members under my control and will ensure that all trial staff members have access to copies of this protocol and to all information relating to preclinical and prior clinical experience (e.g., Investigator's Brochure), ICH GCP "ICH Topic E6", R2, local regulations and the Declaration of Helsinki to enable them to work in accordance with the provisions of these documents.
I will use only the informed consent form approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and will fulfil all responsibilities for submitting pertinent information to the IRB/IEC responsible for this trial.
I agree that Helsinn or its representatives and any local and foreign regulatory authorities shall have access to any source documents from which CRF information may have been generated.
I agree that all documentation supplied to me by Helsinn and CROSS Research SA, Phase I Unit, Switzerland concerning this trial will be kept in the strictest confidence.

Milko Radicioni, MD

CROSS Research SA, Phase I Unit, Switzerland

2.3 CRO

CROSS Research S.A., Switzerland

Coordination

Clinical Study Protocol Author

Biometry Unit Representative

Quality Assurance Unit Representative

3 STUDY SYNOPSIS

Title: A phase I, open label, single dose, two parts study in male and female healthy subjects to assess the safety and pharmacokinetics of Fosnetupitant 235 mg administered as IV bolus and of derived Netupitant and Netupitant metabolites
Protocol number: CRO-PK-22-363 - Sponsor code PNET-22-08
Clinical phase: Phase I
Study design: Open label, single dose, two parts (part A and part B), safety and pharmacokinetics phase I study. Study Part B will be conducted according to a randomized cross-over design
Planned nr. of centers / countries: 1 / Switzerland
Investigator and center: Milko Radicioni, MD - CROSS Research Phase I Unit, Via F. A. Giorgioli 14, CH-6864 Arzo, Switzerland
Investigational products: TEST (T): Intravenous (IV) fosnetupitant 235 mg free base 20 mL ready to use solution for intravenous administration, Patheon Italia S.p.A., Italy REFERENCE (R): IV Akynzeo (235 mg fosnetupitant/0.25 mg palonosetron) in 20 mL injectable solution (Baxter Oncology GmbH, Germany) PLACEBO (P): 0.9% sodium chloride injection solution ready to use solution for intravenous administration (placebo), commercially available product purchased from the market
Dose regimens: **Part A** of the study: In cohort 1, 10 healthy volunteers (HV) will receive a dose of T as a one single 30-min IV infusion and additional 10 subjects will receive a single IV dose of undiluted R (treatment Rα) as a one single 30-min IV infusion of 20 mL, according to a parallel group design. In each of 3 consecutive cohorts - 2, 3 and 4, - 10 healthy volunteers (HV) will receive a single IV dose of T and will be sequentially treated as subgroups of 3, 3, and 4 subjects, respectively. A staggered approach with decreasing infusion time duration will be applied to the injection of T in cohorts 2, 3 and 4. Therefore, in each cohort, the T injection duration will vary as follows: Cohort 1: 30 min (T or Rα) Cohort 2: 15 min (T) Cohort 3: 5 min (T) Cohort 4: 2 min (T) At the end of cohort 1 and of each subgroup of cohorts 2, 3 and 4, safety and tolerability results will be evaluated by the Investigator and the study Sponsor Medical Expert. Predefined stopping rules will be considered for deciding about continuing with the next cohort and a shorter injection duration. If the safety data obtained from a treated cohort are considered as not sufficient for taking a decision on the infusion duration de-escalation process and if additional safety data are deemed necessary to allow such decision to be taken, the study Investigator and the Sponsor Medical Expert may decide to add additional subjects (up to a maximum of 4 subjects per cohort) to the 10 subjects of the treated cohort. After cohort 1, if the injection duration of 30 min of T proves to be safe and well tolerated, 15 min will be tested in cohort 2. After cohort 2, if the injection duration of 15 min proves to be safe and well-tolerated, 5 min will be tested in cohort 3. After cohort 3, if the injection duration of 5 min proves to be safe and well-tolerated, 2 min will be tested in cohort 4. At the end of study Part A, the Sponsor will take a final decision whether to proceed with study Part B with the resulting shortest injection duration considered as adequate in terms of safety determined in study Part A. **Part B** of the study will follow a 2-way, cross-over randomized design and will include 40 male and female subjects. Before entering the crossover phase, each subject will receive P at the shortest infusion duration

STUDY SYNOPSIS (cont.)

Dose regimens (continued):
determined in study Part A. Afterwards, in 2 consecutive crossover periods, each subject will receive T at the shortest injection duration considered as safe and well tolerated, determined in study part A, and 20 mL of solution of R diluted to 50 mL with 0.9% sodium chloride injection solution and infused in 30 min.

Objectives:

Primary objective of Part A:

- To define the shortest safe and tolerable duration of IV injection of T among 4 durations tested in decreasing order: 30, 15, 5 and 2 min, respectively. The selected shortest (safe and tolerable) injection duration determined in part A will be considered for testing in study Part B.

Secondary objective of Part A:

- to characterize the pharmacokinetic profile in plasma of fosnetupitant, netupitant and netupitant metabolites M1, M2 and M3 after injection of T administered at the relevant injection duration and after injection of undiluted R (defined as Rα).
- to determine the safety and tolerability of T administered at the relevant injection duration.

Primary objective of Part B:

- To investigate the exposure equivalence of T, at the shortest injection duration defined as safe in Part A, and R, administered as a 30 min diluted infusion. The equivalence in exposure will be estimated in terms of extent of exposure to netupitant ($AUC_{0-\infty}$ and AUC_{0-t}).

Secondary objectives of Part B:

- To characterize the pharmacokinetic profile in plasma of fosnetupitant, netupitant and netupitant metabolites M1, M2 and M3 after administration of T at the shortest injection duration defined as safe in Part A and R administered as 30 min diluted infusion.
- To confirm the safety and tolerability of T administered at the shortest injection duration defined as safe in Part A in comparison to R, administered as a 30 min diluted infusion.
- To assess the effect of T on ECG parameters (HR, QT, QTcF, QTcB, PR and QRS intervals).
- To assess the effects of the administration of fosnetupitant on the QT interval in the shortest infusion time (defined in Part A) compared to placebo, in male and female healthy subjects.

Endpoints

Primary endpoint of Part A

- Type, number and frequency of treatment-emergent adverse events collected up to 24 h post-dose.

Primary endpoint of Part B

- Area under the plasma concentration-time curve of netupitant from time zero to the time of last measurable concentration or to infinity (AUC_{0-t} and $AUC_{0-\infty}$) following administration of T, at the infusion duration selected in Part A, and R administered as 30-min diluted infusion.

Secondary safety endpoints of Part A

- Vital signs (blood pressure, pulse rate), 12-lead ECG, clinical laboratory tests (blood chemistry, hematology and urinalysis), body weight and physical examination

Secondary safety endpoints of Part B

- Safety and tolerability parameters of T versus R (treatment-emergent adverse events, vital signs [blood pressure, pulse rate], 12-lead ECG, clinical laboratory tests (blood chemistry, hematology and urinalysis), body weight and physical examination.
- Cardiac evaluation:
  - Placebo-corrected change from baseline in HR, QT, QTcF, QTcB, PR and QRS intervals.
  - Change from baseline in HR, QT, QTcF, QTcB, PR and QRS intervals.
  - Categorical outliers for HR, QT, QTcF, QTcB, PR, and QRS intervals.
  - Frequency of changes in T-wave morphology and U-wave presence from triplicate 12-lead ECGs extracted from continuous recordings.

STUDY SYNOPSIS (cont.)

Endpoints (continued)

Secondary PK endpoints of Part A and B

For plasma fosnetupitant, netupitant and its main metabolites M1, M2 and M3, when applicable:

- C_0, C_{max}, t_{max}, C_{last}, t_{last}, AUC_{0-t} (for all analytes with exception of netupitant AUC_{0-t} in Part B, which is the primary endpoint), AUC_{0-24}, λ_z, $t_{½}$, CL, V_z, MRT

Secondary PK endpoints of Part B only

For plasma fosnetupitant, netupitant and its main metabolites M1, M2 and M3, when applicable:

- AUC_{0-120}, $AUC_{0-\infty}$ (with exception of netupitant $AUC_{0-\infty}$, which is the primary endpoint)

For plasma fosnetupitant:

- $RAUC_{fos/netu}$

For plasma M1:

- $RAUC_{M1/netu}$

For plasma M2:

- $RAUC_{M2/netu}$

For plasma M3:

- $RAUC_{M3/netu}$

Analytics: Fosnetupitant, netupitant and its main metabolites M1, M2 and M3 will be determined in plasma samples at a qualified bioanalytical laboratory to Ardena Bioanalysis BV, W. A. Scholtenstraat 7, NL-9403 AJ Assen, the Netherlands. Validated liquid chromatography-tandem mass spectrometry methods with appropriate lower limits of quantification will be used for the determination of plasma concentrations.

Safety and tolerability assessments: Treatment-emergent adverse events; vital signs (blood pressure, HR), physical examinations; laboratory tests; 12-lead ECG and body weight.

Sample size: The planned number of 20 healthy subjects to be included in cohort 1 and 10 healthy subjects to be included in each following cohort of Part A of the study was not computed by statistical assumptions.
The sample size for the netupitant exposure equivalence (netupitant AUC) assessment in Part B of the study will be 40 healthy male and female subjects in order to have 34 completed subjects. Drop-outs will not be replaced. The sample size was determined by a statistical power calculation to test equivalence based on AUC_{0-t}. The assumptions are that the expected ratio of means is 1 (Fosnetupitant 235 mg IV versus Akynzeo IV injection), the cross-over ANOVA √MSE (ln scale) is 0.265, and α is 10% (bilateral). A sample size in each sequence group of 17 (total sample size is 34) is required to have a power of 90%.

Selection criteria: Inclusion criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age:* healthy men/women volunteers, 18-55 years old (inclusive)
3. *Body Mass Index (BMI):* 18.5-30 kg/m^2 inclusive
4. *Vital signs:* systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, pulse rate 50-99 bpm, measured after 5 min at rest in the sitting position
5. *Full comprehension:* ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
6. *Contraception and fertility (women only):* women of childbearing potential defined as a non-menopausal woman who has not had a bilateral oophorectomy or medically documented ovarian failure and/or at risk for pregnancy must agree, signing the informed consent form, to use a highly effective method of contraception throughout the study and to continue for 14 days after the last dose of the study treatment.
   Highly effective contraceptive measures include:
   a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit.
   b. A non-hormonal intrauterine device (IUD) for at least 2 months before the screening visit
   c. A sterile or vasectomized sexual partner
   d. True (long-term) heterosexual abstinence, defined as refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject, while periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), lactational amenorrhea and withdrawal are not acceptable.

STUDY SYNOPSIS (cont.)

Selection criteria (continued):

Women of non-child-bearing potential or in post-menopausal status defined as such when there is either:

a. 12 months of spontaneous amenorrhea or
b. 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or
c. 6 weeks documented postsurgical bilateral oophorectomy with or without hysterectomy

will be admitted.

For all women, pregnancy test result must be negative at screening and admission (Day -1).

7. *Contraception (men only)*: men will either be sterile or agree to use one of the following approved methods of contraception from the first study drug administration until at least 14 days after the last administration, also in case their partner is currently pregnant:
   a. A male condom with spermicide
   b. A sterile sexual partner or a partner in post-menopausal status for at least one year
   c. Use by the female sexual partner of an IUD, a female condom with spermicide, a contraceptive sponge with spermicide, a diaphragm with spermicide, a cervical cap with spermicide, or hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit

   Men must accept to inform their partners of the participation in the clinical study. Furthermore, they will not donate sperm from the date of the informed consent form's signature, throughout the study, and for at least 14 days after the last dose of the study treatment. These requirements are based upon the availability and results of reproductive toxicity data.

Exclusion criteria:

1. *12-leads Electrocardiogram (ECG) (supine position)*: clinically significant abnormalities at screening. With regards to QTc, the following will be considered as exclusion criterion: mean corrected QT (QTcF) > 450 ms. HR < 50 or > 99 bpm. PR < 100 or >220 ms. QRS > 120 ms. Relevantly abnormal T-wave patterns
2. *Physical examination findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. *Laboratory analyses*: clinically significant abnormal laboratory values at screening, indicative of physical illness or suggesting the subject's exclusion, in his/her best interest
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
5. *Diseases*: significant history, in the opinion of the Investigator, of renal, hepatic, gastrointestinal, cardiovascular (in particular, heart failure, hypokalemia, family history of Long QT Syndrome, 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. *Medications*: medications, including over the counter medications and herbal remedies in the 2 weeks before the first visit of the study. Hormonal contraceptives for women are allowed
7. *CYP3A4 inducers and inhibitors*: use of any inducer or inhibitor of CYP3A4 enzymes (drugs, food, herbal remedies) in the 28 days or in the 7 days, respectively, before the planned first study drug administration and during the whole study
8. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
9. *Blood donation or significant blood loss*: blood donations or significant blood loss in the 3 months before the first visit of this study
10. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2020-2025], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
11. *Drug test*: positive result at the urine drug screening test at screening or Day -1
12. *Alcohol test*: positive salivary alcohol test at Day -1
13. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before screening; vegetarians
14. *Pregnancy (women only)*: positive or missing pregnancy test at screening or Day -1, pregnant or lactating women
15. *Netupitant studies*: enrolment in a previous study of netupitant or fosnetupitant (alone or in combination with palonosetron)

STUDY SYNOPSIS (cont.)

Study procedures of Part A:			
	Day	**Procedures/Assessments**	**Notes**
Screening – visit 1	*From Day -21 to Day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number assignment (as S001, S002, etc.) ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, body mass index, vital signs, physical abnormalities) ➢ Triplicate 12-lead ECG recording ➢ Laboratory analyses: hematology, blood chemistry, urinalysis and virology ➢ Serum pregnancy test (women only) ➢ Urine multi-drug screening test ➢ Adverse events recording ➢ Inclusion/exclusion criteria evaluation	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the Phase I Unit source document only and will not be transferred to the Sponsor
Visit 2	*Day -1*	➢ Short physical examination (only if screening physical examination performed more than 7 days before Day -1) ➢ Recording of concomitant medications ➢ Salivary alcohol test ➢ Urine pregnancy test (women only) ➢ Urine multi-drug screening test ➢ Body weight ➢ Vital signs measurement ➢ Adverse events recording ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment ➢ Subject study number assignment (as 001, 002, etc.)	Arrival at the Phase I Unit in the evening Confinement until the morning of Day 2 Standardized low-fat dinner Fasting for 10 h (overnight)
Visit 3	*Day 1*	➢ T or Rα treatment ➢ Vital signs measurement: at pre-dose, at the end of injection, then at 1, 2 and 4 h after end of administration ➢ Triplicate 12-lead ECG recording: at pre-dose, at the end of the injection and 1, 2 and 4 h after the end of the injection ➢ Blood sample collection for pharmacokinetic analysis. See schedule in tabular format: Table 4.4 ➢ Recording of concomitant medications ➢ Adverse events recording	Standardized lunch at least 5 h post-dose (at around 13:00) Standardized dinner at least 12 h post-dose (at around 20:00)
	Day 2	➢ Vital signs measurement at 24 h after end of administration ➢ Triplicate 12-lead ECG recording at 24 h after the end of the injection ➢ Blood sample collection for pharmacokinetic analysis. See schedule in tabular format: Table 4.4 ➢ Recording of concomitant medications ➢ Short physical examination upon discharge ➢ Adverse events recording	Discharge from the Phase I Unit in the morning after the 24-h post-dose blood sample collection, ECG recording and vital signs check

STUDY SYNOPSIS (cont.)

Study procedures of Part A:			
	Day	**Procedures/Assessments**	**Notes**
Visit 4 - Final Visit/ETV	*Day 7 / at ETV in case of discontinuation*	➢ Full physical examination (body weight and physical abnormalities) ➢ Recording of concomitant medications ➢ Vital signs measurement ➢ Triplicate 12-lead ECG recording ➢ Urine pregnancy test (women only) ➢ Laboratory analyses as at screening, except for virology ➢ AE recording In case of clinically significant results at the final visit, the subjects will be followed-up by the Investigator until the normalization of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions
In Part A, treatment emergent adverse events collected up to 24 h after the end of the injection (Visit 3, Day 2) will be evaluated by the Investigator and the Study Sponsor Medical Expert. At the end of cohort 1 and of each subgroup of cohorts 2, 3 and 4, safety and tolerability results will be evaluated by the Investigator and the study Sponsor Medical Expert. Predefined stopping rules will be considered for decision about the treatment of the next cohort of subjects with a shorter injection duration. If the safety data obtained from a treated cohort are considered as not sufficient for taking a decision on the infusion duration de-escalation process, and if additional safety data are deemed necessary to allow such decision to be taken, the study Investigator and the Sponsor Medical Expert may decide to add additional subjects (up to a maximum of 4 subjects per cohort) to the 10 subjects of the treated cohort. The shortest injection duration selected on the basis of the safety and tolerability results of **Part A** will be used in **Part B.**			
Study procedures of Part B:			
	Day	**Procedures/Assessments**	**Notes**
Screening – visit 1	*From Day -21 to Day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number assignment (as S101, S102, etc.) ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, body mass index, vital signs, physical abnormalities) ➢ Triplicate 12-lead ECG recording ➢ Laboratory analyses: hematology, blood chemistry, urinalysis and virology ➢ Serum pregnancy test (women only) ➢ Urine multi-drug screening test ➢ Adverse events recording ➢ Inclusion/exclusion criteria evaluation	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the Phase I Unit source document only and will not be transferred to the Sponsor
Visit 2	*Day -1*	➢ Short physical examination (only if screening physical examination performed more than 7 days before Day -1) ➢ Recording of concomitant medications ➢ Salivary alcohol test ➢ Urine multi-drug screening test ➢ Urine pregnancy test (women only) ➢ Body weight ➢ Adverse events recording ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and randomization ➢ Randomization number assignment (as 101, 102, etc.)	Arrival at the Phase I Unit in the evening Confinement until the morning of Day 5 Standardized low-fat dinner Fasting for 10 h (overnight)

STUDY SYNOPSIS (cont.)

Study procedures of Part B (continued):			
	Day	**Procedures/Assessments**	**Notes**
Visit 3	*Day 1*	➢ P treatment ➢ Vital signs measurement: at pre-dose, end of the infusion, then at 1, 2 and 4 h after the end of the infusion ➢ Continuous 12-lead ECG recording: starting 1 h before administration and up to 48 h after the end of the infusion; discrete triplicate 12-lead ECGs to be extracted 3 times within 1 h before the start of infusion and at the end of the infusion and 0.5, 1, 2 and 4 h after the end of the infusion ➢ Triplicate 12-lead ECG recording: at pre-dose and at 1 and 2 h after the end of infusion ➢ Recording of concomitant medications ➢ Adverse events recording	Standardized lunch at least 5 h post-dose (at around 13:00) Standardized dinner at least 12 h post-dose (at around 20:00)
	Day 2	➢ Vital signs measurement at 24 h after the end of the infusion ➢ Continuous 12-lead ECG recording: continuing up to 48 h after the end of the infusion; discrete triplicate 12-lead ECGs to be extracted at 24 h after the end of the infusion ➢ Triplicate 12-lead ECG recording at 24 h after the end of infusion ➢ Recording of concomitant medications ➢ Adverse events recording	Standardized breakfast, lunch and low-fat dinner at about 08:00, 13:00 and 20:00 and then fasting for 10 h (overnight)
	Day 3	➢ T or R treatment ➢ Vital signs measurement: at pre-dose, end of the injection/infusion, then at 1, 2 and 4 h after the end of the injection/infusion ➢ Continuous 12-lead ECG recording: starting shortly before T/R administration and up to 48 h after the end of the injection/infusion; discrete triplicate 12-lead ECGs to be extracted 3 times within 1 h before the start of injection/infusion and at the end of the injection/infusion and 0.5, 1, 2 and 4 h after the end of the injection/infusion ➢ Triplicate 12-lead ECG recording: at pre-dose and at 1 and 2 h after the end of T/R injection/infusion ➢ Recording of concomitant medications ➢ Blood sample collection for pharmacokinetic analysis. See schedule in tabular format: Table 4.4 ➢ Adverse events recording	Standardized lunch at least 5 h post-dose (at around 13:00) Standardized dinner at least 12 h post-dose (at around 20:00)
	Day 4	➢ Vital signs measurement at 24 h after the end of T/R injection/infusion ➢ Continuous 12-lead ECG recording: continuing up to 48 h after the end of T/R injection/infusion; discrete triplicate 12-lead ECG to be extracted at 24 h after the end of T/R injection/infusion ➢ Triplicate 12-lead ECG recording at 24 h after the end of T/R injection/infusion ➢ Recording of concomitant medications ➢ Blood sample collection for pharmacokinetic analysis. See schedule in tabular format: Table 4.4 ➢ Adverse events recording	Standardized breakfast, lunch and dinner at around 08:00, 13:00 and 20:00

STUDY SYNOPSIS (cont.)

Study procedures of Part B (continued):			
	Day	**Procedures/Assessments**	**Notes**
Visit 3 (continued)	*Day 5*	➢ Vital signs measurement at 48 h after the end of T/R injection/infusion ➢ Continuous 12-lead ECG recording: continuing up to 48 h after the end of T/R injection/infusion; discrete triplicate 12-lead ECG to be extracted at 48 h after the end of T/R injection/infusion ➢ Recording of concomitant medications ➢ Blood sample collection for pharmacokinetic analysis. See schedule in tabular format: Table 4.4 ➢ Adverse events recording	Discharge from the Phase I Unit in the morning after the 48-h post-dose blood sample collection, ECG recording and vital signs check
Visit 4	*Day 6*	➢ Blood sample collection for pharmacokinetic analysis: 72 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	Ambulatory visit. Arrival at the Phase I Unit in the morning.
Visit 5	*Day 7*	➢ Blood sample collection for pharmacokinetic analysis: 96 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 4
Visit 6	*Day 8*	➢ Blood sample collection for pharmacokinetic analysis: 120 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 4
Visit 7	*Day 9*	➢ Blood sample collection for pharmacokinetic analysis: 144 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 4
Visit 8	*Day 10*	➢ Blood sample collection for pharmacokinetic analysis: 168 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 4
Visit 9	*Day 11*	➢ Blood sample collection for pharmacokinetic analysis: 192 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 4
Visit 10	*Day 12*	➢ Blood sample collection for pharmacokinetic analysis: 216 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 4

STUDY SYNOPSIS (cont.)

Study procedures of Part B (continued):			
	Day	**Procedures/Assessments**	**Notes**
Visit 11	*Day 13*	➢ Blood sample collection for pharmacokinetic analysis: 240 h post-dose ➢ Recording of concomitant medications ➢ Short physical examination ➢ Laboratory analyses as at screening, except for virology ➢ Vital signs measurement ➢ Triplicate 12-lead ECG recording ➢ Urine pregnancy test (women only) ➢ Adverse events recording	As visit 4
Wash-out	*At least 28 days*	A wash-out interval of at least 28 days will elapse between the two administrations of active treatment (T and R) of the two study periods (Day 3 of period 1 and Day 1 of period 2)	
Visit 12	*Day -1*	➢ Short physical examination ➢ Recording of concomitant medications ➢ Salivary alcohol test ➢ Urine multi-drug screening test ➢ Urine pregnancy test (women only) ➢ Body weight ➢ Laboratory analyses as at screening, except for virology ➢ Adverse events recording	As visit 2
Visit 13	*Days 1-3*	As Days 3-5 of visit 3. T or R treatment according to the randomization list and cross-over design	As Days 3-5 of visit 3
Visit 14	*Day 4*	➢ Blood sample collection for pharmacokinetic analysis: 72 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	Ambulatory visit. Arrival at the Phase I Unit in the morning.
Visit 15	*Day 5*	➢ Blood sample collection for pharmacokinetic analysis: 96 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 14
Visit 16	*Day 6*	➢ Blood sample collection for pharmacokinetic analysis: 120 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 14
Visit 17	*Day 7*	➢ Blood sample collection for pharmacokinetic analysis: 144 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 14

STUDY SYNOPSIS (cont.)

Study procedures of Part B (continued):			
	Day	**Procedures/Assessments**	**Notes**
Visit 18	*Day 8*	➢ Blood sample collection for pharmacokinetic analysis: 168 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 14
Visit 19	*Day 9*	➢ Blood sample collection for pharmacokinetic analysis: 192 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 14
Visit 20	*Day 10*	➢ Blood sample collection for pharmacokinetic analysis: 216 h post-dose ➢ Vital signs measurement ➢ Recording of concomitant medications ➢ Adverse events recording	As visit 14
Visit 21 - Final Visit/ETV	*Day 11 of period 2 / at ETV in case of discontinuation*	➢ Blood sample collection for pharmacokinetic analysis: 240 h post-dose ➢ Laboratory analyses as at screening, with the exception of virology ➢ Vital signs measurement ➢ Triplicate 12-lead ECG recording ➢ Urine pregnancy test (women only) ➢ Full physical examination (body weight and physical abnormalities) ➢ Recording of concomitant medications ➢ Adverse events recording In case of clinically significant results at the final visit, the subjects will be followed-up by the Investigator until the normalization of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions

Diet and lifestyle:
In Part A, the subjects will be confined from the evening preceding T or Rα (undiluted R) treatment (study Day -1) until the morning of Day 2. In Part B, the subjects will be confined from the evening preceding P treatment (study Day -1) until the morning of Day 5 in period 1 and from the evening preceding T or R treatment (study Day -1) until the morning of Day 3 in period 2. All other study visits will be ambulatory.
During the subjects' confinement at the Phase I Unit, they will not take any food or drinks (except water) for about 10 h (i.e., overnight) before P, T or R. Water will be allowed as desired, except for 1 h before and 1 h after P, T or R administration start. In order to maintain adequate hydration, the subjects will be encouraged to drink at least 180 mL of still mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.
On Day 1 (T or Rα administration day) of Part A, on Day 1 in both periods of Part B (P administration day in period 1, T or R administration day in period 2) and on Day 3 of period 1 of Part B (T or R administration day), the subjects will remain fasted until 5 h post-dose.
One cup of coffee or tea will be allowed after each meal only; any other coffee, tea or food containing xanthines (i.e., coke, energy drinks, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement. In particular, grapefruit and any other food or beverage known to interfere with cytochrome P450 will be forbidden for 7 days (168 h) before the first study treatment administration until the end of the study. During confinements, smoking will be forbidden, and routine ambulant daily activities will be strongly recommended.

STUDY SYNOPSIS (cont.)

Data analysis:
The pharmacokinetic analysis and the statistical analysis of pharmacokinetic parameters will be performed at the Biometry Unit of the CRO using Phoenix WinNonlin® version 8.3.5 or higher, Certara, Princeton, NJ, USA and SAS® version 9.3 (TS1M1) for Windows® or higher. The statistical analysis of safety data will be performed using SAS® version 9.3 (TS1M1) for Windows® or higher.
The pharmacokinetic parameters of fosnetupitant, netupitant and its metabolites will be calculated using a non-compartmental analysis (NCA) and will be summarized using descriptive statistics.
At study Part B only, bioequivalence of T selected in Part A and R will be evaluated by analysis of variance (ANOVA) of log-transformed netupitant AUC_{0-t}. and $AUC_{0-\infty}$. The statistical analysis will take into account treatment, period, sequence and subject within sequence as fixed effects.
The parametric point estimator, i.e., the T/R netupitant AUC_{0-t} and $AUC_{0-\infty}$ geometric mean ratio, and the 90% confidence interval (CI) will be calculated using the adjusted least squares means from the ANOVA. Results for the log-transformed exposure measures (AUC_{0-t} and $AUC_{0-\infty}$.) will be back-transformed to obtain point estimators (i.e., geometric mean ratio) and two-sided 90% CI as percentages.
Bioequivalence of the selected T and R will be claimed if the 90% CI for the geometric mean ratio of netupitant AUC_{0-t} and $AUC_{0-\infty}$ is entirely contained within the bioequivalence interval of 80.00% - 125.00%.
The peak time, t_{max}, of T and R will be analyzed using a non-parametric test applied to untransformed data.

4 STUDY SCHEDULE

Table 4.1 Study procedures of Part A

ACTIVITIES	Screening	Admission	Active treatment administration	Observation and release	Final visit or ETV[8]
Visit	**V1**	**V2**	**V3**		**V4 or ETV[8]**
Day	**-21 to -2**	**-1**	**1**	**2**	**7**
Informed consent	x				
Inclusion/Exclusion criteria	x	x			
Full physical examination	x				x
Short physical examination		x[1]		x	
Demographics	x				
Medical and surgical history	x				
Previous and concomitant treatments	x	x	x	x	x
Height and body mass index (BMI)	x				
Body weight	x	x			x
Safety laboratory (hematology, blood chemistry, urinalysis)	x				x
Virology (HBs Ag, HCV Ab, HIV)	x				
Pregnancy test	x[2]	x[3]			x[3]
Urine drug screen	x	x			
Salivary alcohol test		x			
Triplicate 12-lead ECGs	x		x[4]	x[6]	x
Vital signs	x	x	x[5]	x[6]	x
Enrolment		x			
Confinement		x	x		
Active Treatment administration			x		
PK blood sampling[7]			x ---------- x		
Discharge				x	
AE recording[9]	x	x	x	x	x

1. *Only if screening full physical examination performed more than 7 days before Day -1*
2. *Women only - serum b-HCG test*
3. *Women only - urine test*
4. *At pre-dose, at the end of injection, then at 1, 2, 4 and 24 h after end of administration; to be measured after 5 min at rest in supine position before recording.*
5. *At pre-dose, at the end of the injection, then at 1, 2, 4 and 24 h after the end of the injection; to be measured after 5 min at rest in sitting position before measurement.*
6. *Upon discharge at 24 h after the end of active treatment injection.*
7. *See schedule in tabular format (Table 4.4)*
8. *Early termination visit (ETV) upon discontinuation in case of premature termination*
9. *AEs monitored starting at the screening visit, immediately after informed consent, up to the final visit or ETV*

Table 4.2 Study procedures of Part B

ACTIVITIES	Screening		Period 1				Period 2			Final Visit[14] or ETV[15]
VISIT	V1	V2	V3		V4-V11		V12	V13	V14-20	V21 or ETV
DAY(s)	-21 to -2	-1	1-2	3-5	6 - 13		-1	1-3	4-10	11[14] or ETV[15]
Informed consent	x					*28-days wash-out completion*				
Inclusion/Exclusion criteria	x	x								
Demographics	x									
Medical/Surgical history	x									
Full physical examination	x									x
Short physical examination		x[1]			x[10]		x			
Previous and concomitant treatments	x	x	x	x	x		x	x	x	x
Height and body mass index (BMI)	x									
Body weight	x	x					x			x
Laboratory (hematology, blood chemistry, urinalysis)	x				x[10]		x			x
Virology (HBs Ag, HCV Ab, HIV)	x									
Pregnancy test	x[2]	x[3]			x[3, 10]		x[3]			x[3]
Urine drug screening	x	x					x			
Salivary alcohol test		x					x			
Vital signs	x		x[4]	x[5]	x		x	x[5]	x	x
Triplicate 12-lead ECGs for immediate safety	x		x[6]	x[7]	x[10]			x[7]		x
Continuous ECG monitoring			x[8]	x[9]				x[9]		
Eligibility evaluation		x								
Confinement		x	x	x			x	x		
Randomization		x								
Placebo administration			x[16]							
Active treatment administration				x[17]				x[16]		
PK blood sampling[11]				x	x			x	x	x
Discharge[12]				x				x		x
AEs monitoring[13]	x	x	x	x	x		x	x	x	x

1. *At visit 2, only if screening physical examination performed more than 7 days before Day -1*
2. *Women only - serum b-HCG test*
3. *Women only - urine test*
4. *At pre-dose, end of the injection/infusion, then at 1, 2, 4 and 24 h after the end of the injection/infusion; to be measured after 5 min at rest (sitting position).*
5. *At pre-dose, end of the injection/infusion, then at 1, 2, 4, 24 and 48 h after the end of the injection/infusion; to be measured after 5 min at rest (sitting position).*
6. *At pre-dose and at 1, 2 and 24 h after the end of P injection/infusion; to be measured after subjects remained for 5 min at rest in supine position before recording.*
7. *At pre-dose and at 1, 2 and 24 h after the end of T/R injection/infusion; to be measured after subjects remained for 5 min at rest in supine position before recording.*
8. *Starting 1 h before P administration and up to 48 h after the end of the injection/infusion; discrete triplicate 12-lead ECGs to be extracted 3 times within 1 h before the start of injection/infusion and at the end of the injection/infusion and 0.5, 1, 2, 4 and 24 h after the end of the injection/infusion after 10 min at rest in supine position*
9. *Starting shortly before T/R administration and up to 48 h after the end of the injection/infusion; discrete triplicate 12-lead ECGs to be extracted 3 times within 1 h before the start of injection/infusion and at the end of the injection/infusion and 0.5, 1, 2, 4, 24 and 48 h after the end of the injection/infusion after 10 min at rest in supine position*
10. *On Day 13 only*
11. *See schedule in Table 4.4*
12. *In the morning after the 48-h post-dose blood sample collection, ECG recording and vital signs check*
13. *Starting at the screening visit, immediately after informed consent, up to the final visit/ETV*
14. *After the 240-h post-dose blood sampling on Day 11 of Period 2.*
15. *Upon discontinuation, in case of early termination*
16. *On Day 1*
17. *On Day 3*

Table 4.3 Tolerance ranges for the vital signs and ECG recording for immediate safety evaluation of Part A

Scheduled time	Tolerance range
Pre-dose (0) of Day 1	2 h before the start of the injection/infusion
At the end of injection/infusion	+10 min
1, 2 h	+10 min
4 h (vital signs)	±1 h
4 h (ECG)	+1 h
24, 48 h (vital signs)	±2 h
24 h (ECG)	+2 h

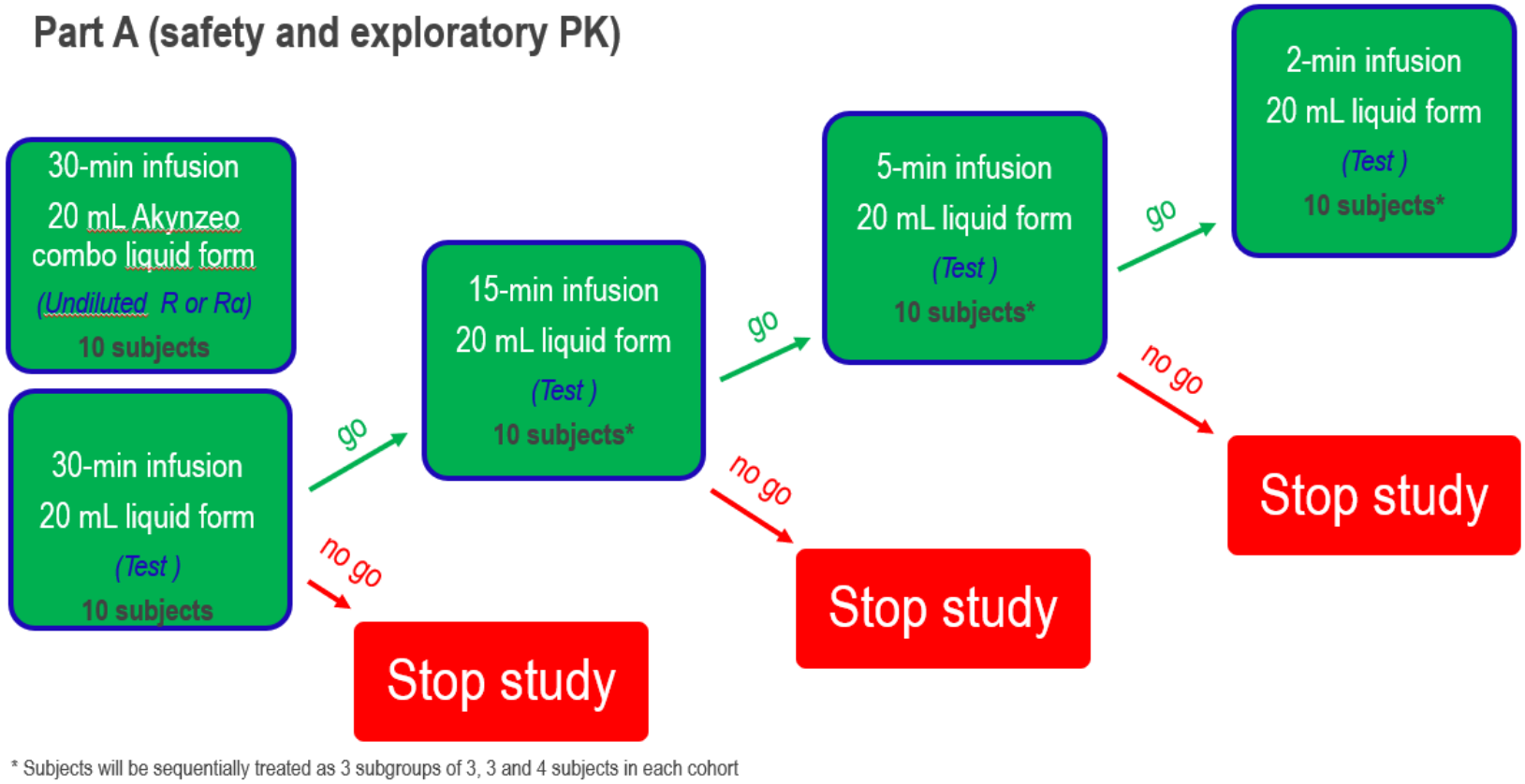
Table 4.4 Schedule of PK blood sampling

	Blood sampling times after the start of T or R treatment									
	T injection of								**Reference product infusion of**	
	2 min		**5 min**		**15 min**		**30 min**		**30 min**	**30 min**
	Part A	**Part B**	**Part A**	**Part B**	**Part A**	**Part B**	**Part A**	**Part B**	**Part A (Rα)**	**Part B (R)**
Pre-dose	X	X	X	X	X	X	X	X	X	X
2 min	X	X								
5 min	X	X	X	X						
10 min	X	X	X	X						
15 min	X	X	X	X	X	X				
20 min	X	X	X	X	X	X				
30 min	X	X	X	X	X	X	X	X	X	X
45 min	X	X	X	X	X	X	X	X	X	X
1 h	X	X	X	X	X	X	X	X	X	X
1.5 h	X	X	X	X	X	X	X	X	X	X
2 h	X	X	X	X	X	X	X	X	X	X
3 h	X	X	X	X	X	X	X	X	X	X
4 h	X	X	X	X	X	X	X	X	X	X
8 h	X	X	X	X	X	X	X	X	X	X
12 h	X	X	X	X	X	X	X	X	X	X
24 h	X	X	X	X	X	X	X	X	X	X
48 h		X		X		X		X		X
72 h		X		X		X		X		X
96 h		X		X		X		X		X
120 h		X		X		X		X		X
144 h		X		X		X		X		X
168 h		X		X		X		X		X
192 h		X		X		X		X		X
216 h		X		X		X		X		X
240 h		X		X		X		X		X

T = Fosnetupitant 235 mg in 20 mL IV injectable solution, administered at predefined time durations (30, 15, 5 and 2 min)
R = Fosnetupitant/palonosetron 235 mg/0.25 mg (IV Akynzeo FDC) 20 mL liquid formulation diluted to 50 mL, and administered in 30 min (Part B)
Rα = Fosnetupitant/palonosetron 235 mg/0.25 mg (IV Akynzeo FDC) 20 mL liquid formulation, undiluted and administered in 30 min (Part A)

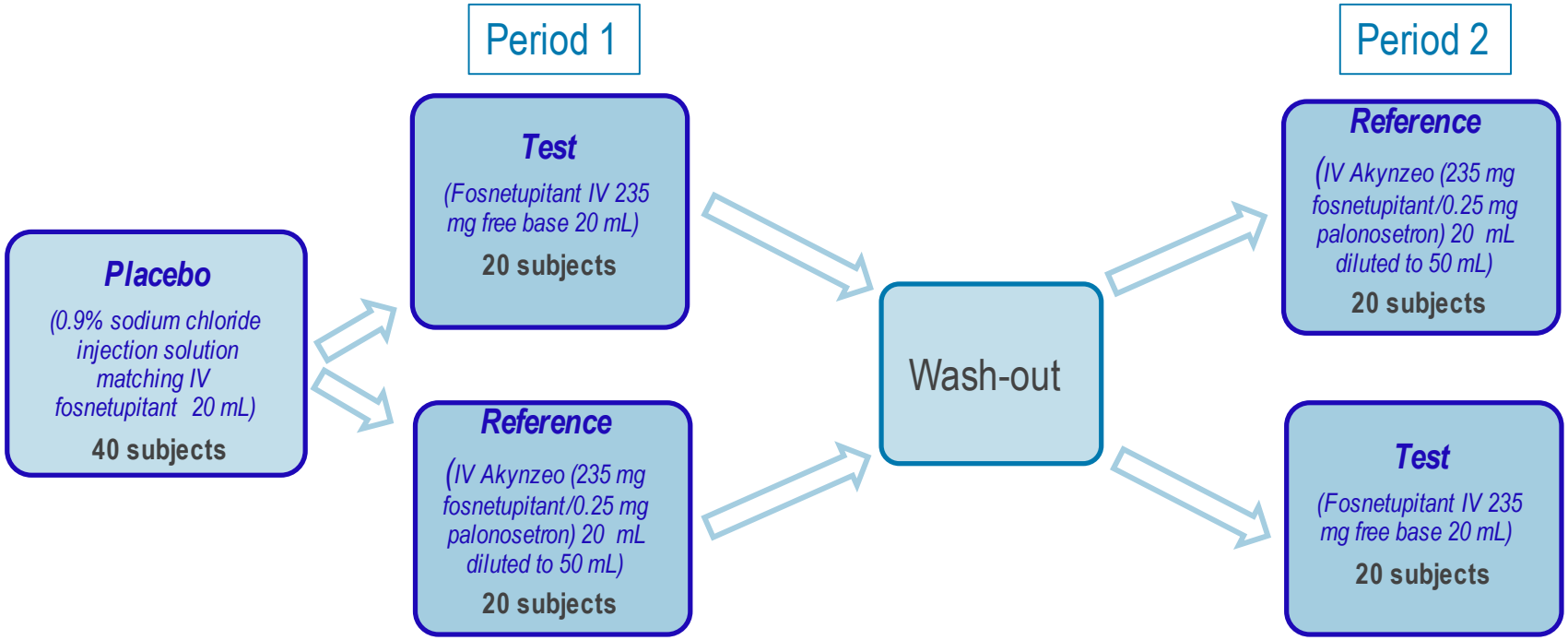
Figure 4.1 Overall study scheme

Study Part A



Study Part B

Safety and PK



5 TABLE OF CONTENTS

5.1 TABLES

5.2 FIGURES

6 LIST OF ABBREVIATIONS

γ-GT	g-Glutamyl Transpeptidase
λz	Terminal rate constant
5-HT_3	5-hydroxytryptamine subtype 3
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
AUC_{0-t}	Area Under the concentration-time Curve from time zero to time t of last measurable concentration
AUC_{0-24}	Area Under the concentration-time Curve from time zero to 24h
AUC_{0-120}	Area Under the concentration-time Curve from time zero to 120h
$AUC_{0-\infty}$	Area Under the concentration vs. time Curve up to infinity
$\%AUC_{extra}$	Percentage of the residual area (C_t/l_z) extrapolated to infinity in relation to the total AUC_{0-inf}
BQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
BW	Body Weight
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CINV	Chemotherapy-Induced Nausea and Vomiting
CL	Systemic clearance
C_{last}	Last measurable plasma concentration above the lower limit of quantification of the bioanalytical method
C_0	Plasma concentration at the end of the injection or infusion
C_{max}	Maximum plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CS	Clinically Significant
CV	Coefficient of Variation
CYP	Cytochrome
EC	Ethics Committee
ECG	Electrocardiogram
ETV	Early Termination Visit
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FSFV	First Subject First Visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
h	hour
HBs Ag	Hepatitis B virus surface antigen

HCV Ab	Hepatitis C virus antibodies
HEC	Highly Emetogenic Chemotherapy
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IMP	Investigational Medicinal Product
IV	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
liq	Liquid
LQL	Lower Quantification Limit
LSLV	Last Subject Last Visit
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MEC	Moderately Emetogenic Chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
N	Normal
MSE	Mean Square Error
NA	Not Applicable
NC	Not Calculated
NDA	New Drug Application
NK-1	Neurokinin-1
OTC	Over The Counter
PE	Point Estimator
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
R	Reference (treatment)
Rα	Reference Alpha (treatment with undiluted R)
RAs	Receptor Antagonists
$RAUC_{M1/netu}$	Molecular weight normalized M1 to netupitant $AUC_{0\text{-}inf}$ ratio
$RAUC_{M2/netu}$	Molecular weight normalized M2 to netupitant $AUC_{0\text{-}inf}$ ratio
$RAUC_{M/netu}$	Molecular weight normalized M3 to netupitant $AUC_{0\text{-}inf}$ ratio
$RAUC_{fos/netu}$	Molecular weight normalized fosnetupitant to netupitant $AUC_{0\text{-}inf}$ ratio.
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SDTM	Study Data Tabulation Model
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test (treatment)

TEAE	Treatment-Emergent Adverse Event
$t_{1/2}$	Half-life
t_{last}	Time of last measurable plasma concentration above the lower limit of quantification of the bioanalytical method
t_{max}	Time to achieve C_{max}
US	United States
USDA	United States Department of Agriculture
V_z	Volume of distribution in the post-distribution phase
WHODDE	World Health Organization Drug Dictionary Enhanced

7 STUDY RESPONSIBLE PERSONS

7.1 Sponsor

Helsinn Healthcare SA, Via Pian Scairolo 9, CH-6912 Lugano - Switzerland
Phone: +41 91 985 21 21
Fax: +41 91 993 21 22
Email:

Study Coordinator:

Medical Expert

Responsible Statistician:

Clinical Pharmacokineticist:

Quality Assurance

Drug Safety Physician:

7.2 Institutes performing the study

7.2.1 Clinical center

CROSS Research SA – Phase I Unit, Via F. A. Giorgioli 14, CH-6864 Arzo, Switzerland
Phone: +41 91 640 44 50
Fax: +41 91 640 44 51
Email: clinic@croalliance.com

Principal Investigator
Milko Radicioni, MD

7.3 Drug assay

Ardena Bioanalysis BV, W. A. Scholtenstraat 7, NL-9403 AJ Assen, the Netherlands
Phone: +31.59.23.44.211
Fax: +31.59.23.44.425

Analytical facilities and procedures are in compliance with GCP and the general principles of GLP regulations.

7.4 Centralized clinical laboratory

Unilabs Ticino, via Rovere 8, CH-6932 Breganzona, Switzerland
Phone: +41.91.960.73.73
Fax: +41.91.960.73.74
Email:

7.5 Continuous ECG provider

Banook Group, 84 Avenue du 20ème Corps, 5400 Nancy, France
Phone: +33.3.83.39.10.10

Responsible person

7.6 Co-ordination, monitoring, data analysis & reporting

CROSS Research S.A.
Via F. A. Giorgioli 14, CH-6864 Arzo, Switzerland

Coordination

Email:

Medical Writing

Email:

Biometry Unit Representative

Email: statistics@croalliance.com

Quality Assurance Unit Representative

Email: qau@croalliance.com

8 INTRODUCTION

8.1 Background

The negative aspects of nausea and vomiting can influence all facets of a cancer patient's life. If nausea and vomiting are not controlled in a cancer patient receiving chemotherapy, they may result in serious metabolic problems such as fluids and electrolytes imbalance and nutritional status disturbances. In addition, uncontrolled nausea and vomiting may also lead to the decision by the patient to stop potentially beneficial cancer therapy.
There are different pharmaceutical agents used to control chemotherapy-induced nausea and vomiting (CINV). However, control of these symptoms is not yet optimal. Thus, the search for newer drugs that would improve these symptoms and patients' ability to tolerate the chemotherapy is still ongoing (1, 2).
The development of two classes of antiemetic drugs contributed to some major recent advances in controlling CINV. The 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonists (RAs) in combination with dexamethasone significantly improved the control of acute post chemotherapy emesis. However, delayed emesis, which may last for several days, was still a challenge with this combination. The control of acute and delayed emesis was improved after neurokinin-1 (NK_1) RAs had been added to the $5\text{-}HT_3$ RAs and steroids combination. Use of an NK_1 RAs with a $5\text{-}HT_3$ inhibitor is therefore considered optimal in the prevention of CINV (3).

The oral NEPA fixed-dose combination (FDC) of netupitant and palonosetron is currently authorized, under the name Akynzeo® in USA, in EU, in Switzerland and in several other countries worldwide. Oral Akynzeo® was approved by the US Food and Drug Administration (FDA) in Oct 2014, for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of chemotherapy, including but not limited to highly emetogenic chemotherapy (HEC). In Europe, oral Akynzeo® was approved in May 2015; the therapeutic indication is the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic chemotherapy (MEC).
In Switzerland, oral Akynzeo® was approved in November 2015, the therapeutic indication is the prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy. Later, the development of an IV FDC of netupitant pro-drug (named fosnetupitant) and palonosetron hydrochloride also began.
Since netupitant is insoluble in water as such, the Sponsor developed fosnetupitant, a water-soluble phosphorylated pro-drug of netupitant, which is rapidly converted into netupitant *in vivo* following intravenous (IV) administration. Fosnetupitant proved to be safe and well tolerated. The pharmacology of fosnetupitant is mainly attributable to netupitant.

IV NEPA FDC was approved in USA in 2018 as Akynzeo® for injection, indicated in prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (NDA 210493). Akynzeo® for injection is a lyophilized powder to be reconstituted and further diluted to 50 mL, to be administered as a 30 min IV infusion, starting 30 min before chemotherapy. The same lyophilized form of IV NEPA was approved in EU in March 2020 (EU/1/15/1001/003) for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic chemotherapy (MEC) (4).

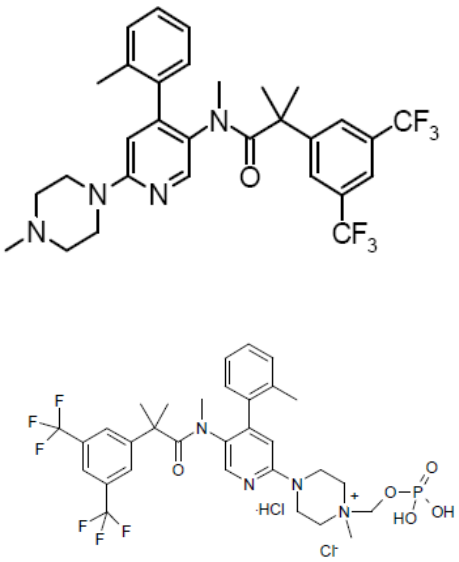
The liquid formulation of IV NEPA was then approved initially in US as a CMC supplement of the Akynzeo® for injection NDA (NDA 210493, S-002) with the same indication of the lyophilized form. IV NEPA liquid formulation has also been authorized by EMA on 12 Nov 2021 as Akynzeo® concentrate for solution for infusion, with the same indications of NEPA Oral and NEPA lyophilized form. The IV NEPA liquid formulation has also been approved in Switzerland on 1 Sep 2022 for the prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy (4).

With respect to the fosnetupitant pharmacology, details are given in the Investigator's Brochure (5).

8.2 Netupitant and Fosnetupitant

Fosnetupitant is rapidly converted to netupitant following IV administration; netupitant is a potent NK_1 RA to be used in combination with other antiemetic drugs against CINV.

Figure 8.2.1 Structural formula of netupitant (top) and fosnetupitant (bottom)



8.2.1 Fosnetupitant pharmacokinetic (PK) profile

In general, fosnetupitant is rapidly converted into netupitant after IV administration, resulting in a limited mean systemic exposure to the pro-drug. The first quantifiable netupitant concentrations are promptly observed after the start of the 30 min IV infusion of the pro-drug. Fosnetupitant C_{max} and AUC increase dose-proportionally with dose increase. Similarly, netupitant peak plasma concentrations increase with ascending IV fosnetupitant doses in a dose-proportional manner, whereas AUC shows a tendency for a higher than dose-proportional increase. The elimination of netupitant is slow and is characterized by a long terminal elimination half-life. Netupitant metabolites are early detected within 1 h from start of fosnetupitant infusion.

IV fosnetupitant chloride hydrochloride dose of 260 mg (corresponding to 235 mg of fosnetupitant free base) proved to be equivalent, in terms of exposure to netupitant, to the oral 300 mg netupitant dose. Indeed, the exposure ($AUC_{0\text{-}inf}$) to netupitant after oral administration of the FDC (containing 300 mg netupitant and 0.5 mg palonosetron) is similar to that obtained after the IV administration of 260 mg fosnetupitant chloride hydrochloride (corresponding to 235 mg of fosnetupitant free base). Netupitant C_{max} (840.8 µg/L) following IV fosnetupitant administration is higher compared to the netupitant C_{max} (477.3 µg/L) achieved after the oral administration of the FDC.

8.2.1.1 Phase I PK studies of fosnetupitant after 30-min IV infusion to healthy volunteers

A Phase I, double-blind, controlled, parallel groups, unbalanced single ascending dose study coded PNET-12-23 was performed to assess the safety of IV administered fosnetupitant combined with cross-over study extensions to estimate the dose of IV fosnetupitant yielding equivalent exposure to netupitant as oral netupitant 300 mg/palonosetron 0.5 mg FDC in healthy male and female volunteers (5). The primary objective of this Phase I study was to assess the safety of fosnetupitant chloride hydrochloride administered as a single 30-min IV infusion in the dose range from 19.5 to 390 mg.
The secondary objective was to estimate the relative availability factor ($F_{rel\ IV}$) for netupitant (based on $AUC_{0\text{-}inf}$) when given in form of IV fosnetupitant chloride hydrochloride in comparison to the oral netupitant 300 mg/palonosetron 0.5 mg FDC; this allowed to identify the IV fosnetupitant chloride hydrochloride dose that yields a netupitant exposure equivalent to that provided by a 300 mg dose of oral netupitant.

All study parts were performed under double-blind (within dose cohorts), double dummy conditions.
A total of 160 subjects were randomized in this study. One hundred and fifty-eight (158) subjects received at least one dose of fosnetupitant IV or netupitant/palonosetron FDC capsule. One hundred fifty-five (155) subjects completed the study. No subject discontinued the study due to treatment emergent adverse events (TEAEs).

Plasma concentrations of fosnetupitant at the end of 30-min infusions ranged, on average, from 553 µg/L, at the lowest dose level (19.5 mg), to 9134 µg/L, at the highest dose level tested (390 mg). Mean fosnetupitant plasma concentrations declined rapidly within the first 2 h after the end of the infusion.

Bi-exponential curves underlie both a rapid fosnetupitant distribution throughout the body and an efficient elimination process, this latter being mainly due to a metabolic hydrolysis that gives rise to netupitant. A clear-cut mono-exponential terminal phase of fosnetupitant appears to emerge from the 2nd hour onwards at the highest doses only, i.e., after administration of the 325 mg and 390 mg doses, whereas at lower doses mixed distribution/elimination phases can be observed from the 1st hour after the end of the infusion up to the time of the last measurable concentration of fosnetupitant (2nd hour after the start of the infusion).

Maximum fosnetupitant concentrations were mainly observed at the end of infusion (median t_{max}: 0.25 h to 0.5 h). The mean systemic exposure increased with ascending doses. Mean $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ ranged respectively from 222 h·µg/L to 4349 h µg/L and from 416 h·µg/L

to 4353 h·µg/L for doses in the interval from 19.5 mg to 390 mg. Mean systemic clearance was very high and ranged from 78.37 to 96.33 L/h, values close to the human liver blood flow. Mean volume of distribution for the pro-drug increased with ascending doses and ranged from 58.3 L (at 65 mg) up to 163.1 L (at 390 mg). The apparent terminal elimination half-life of fosnetupitant chloride hydrochloride ranged from 0.05 h to 1.24 h in the dosing interval from 32.5 mg to 390 mg. At 260 mg, the mean half-life was 0.956 h.

After dose escalation from 19.5 mg to 390 mg fosnetupitant chloride hydrochloride, the first quantifiable netupitant plasma concentrations were detected at all dose levels at mid infusion (15 min). Peak netupitant concentrations were observed at the end of infusion (30 min) at all dose levels. Following infusion of fosnetupitant chloride hydrochloride over 30 min, mean concentrations of netupitant remained nearly at the same level until 4 h and declined slowly afterwards.

Mean C_{max} and mean systemic exposure increased with ascending fosnetupitant chloride hydrochloride doses (mean C_{max} of 66 µg/L and 1310 µg/L, mean AUC_{0-t} of 556 h·µg/L and 19647 h·µg/L, and mean AUC_{0-inf} of 716 h·µg/L and 23923 h·µg/L for 19.5 mg and 390 mg doses, respectively).
The elimination of netupitant was slow with a long apparent terminal elimination half-life that ranged from 21 h to 182 h. Mean $t_{1/2}$ ranged from 35 h to 55 h.
The exposure to netupitant after IV administration of 260 mg fosnetupitant chloride hydrochloride (mean AUC_{0-t} of 12014 h·µg/L and mean AUC_{0-inf} of 13854 h·µg/L) was comparable to the mean systemic exposure to netupitant after oral administration of 300 mg netupitant (mean AUC_{0-t} of 11317 h·µg/L and mean AUC_{0-inf} of 13899 h·µg/L).

The systemic exposure to the 3 netupitant metabolites M1, M2 and M3 also increases with ascending fosnetupitant doses. C_{max} of M2 is higher (mean C_{max}±SD = 178.74±84.52 ng/mL; median t_{max} = 2 h) and is achieved earlier than M1 (mean C_{max}±SD = 23.31±9.26 ng/mL; median t_{max} = 12 h) and M3 (mean C_{max}±SD = 46.49±16.86 ng/mL; median t_{max} = 12 h). All 3 metabolites are eliminated slowly and M1 (mean $t_{1/2}$±SD = 159.54±72.62 h) shows a longer elimination half-life compared to M2 (mean $t_{1/2}$±SD = 136.4±107.06 h) and M3 (mean $t_{1/2}$±SD = 111.4±54.13 h) (5).

8.2.1.2 Phase I PK study of fosnetupitant after 30-min IV infusion to cancer patients

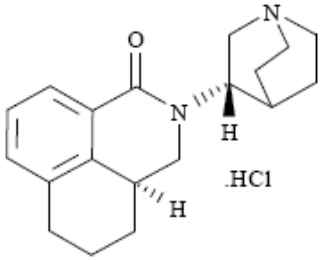
PK of fosnetupitant, netupitant and palonosetron after IV infusion was studied also in 24 adult male and female cancer patients after administration of IV NEPA (study NEPA-15-19) (4). Fosnetupitant was rapidly converted into netupitant after IV administration, resulting in a limited mean systemic exposure to the pro-drug. Exposure to netupitant was similar to that reported in healthy volunteers after a single IV infusion of 260 mg of fosnetupitant chloride hydrochloride and to that observed in healthy volunteers after oral administration of 300 mg of netupitant. This supports the evidence, also in patients, that a 260 mg IV fosnetupitant chloride hydrochloride (corresponding to 235 mg of fosnetupitant) dose yields an exposure to netupitant equivalent to that which follows a 300 mg netupitant oral dose.
Palonosetron PK profile was superimposable to that observed in a previous PK study in healthy subjects in which a 0.25 mg palonosetron dose was administered as an IV bolus, with the obvious exception of C_{max} which was lower after 30-min infusion as compared to the IV bolus.

There were no apparent gender-based differences in PK parameters of fosnetupitant, netupitant, metabolites M1, M2 and M3, and palonosetron.

8.3 Palonosetron

Palonosetron is a potent and selective 5-HT_3 RA with demonstrated efficacy by the IV and oral route for the management of nausea and vomiting associated with cancer chemotherapy. Its prolonged duration of action offers significant advantages over other 5-HT_3 RAs resulting in an extended antiemetic protection. In July 2003 the FDA approved palonosetron 0.25 mg IV as a 30-second bolus for the prevention of acute CINV associated with HEC or MEC, and for prevention of delayed CINV associated with MEC (initial and repeat courses). In Europe, IV palonosetron was approved via the Centralized Procedure in March 2005. Palonosetron 0.50 mg soft gelatine capsules formulation, was approved in the US on August 22, 2008, with the indication in the US o of acute nausea and vomiting associated with initial and repeat courses of MEC. Marketing authorization was granted in the EEA on May 5, 2010, for the prevention of nausea and vomiting associated with MEC in adults. Palonosetron is registered in several countries with different trademarks (Aloxi®, Onicit®, Paloxi®).

Figure 8.3.1 Structural formula of palonosetron



8.4 Safety

Overall, palonosetron proved to have a very good safety profile and was well tolerated across all adult and pediatric studies, both in the IV and the oral formulations (the latter has been tested so far in adults only) and across all geographic regions studied.

In Phase I studies, netupitant administered orally alone or in combination with palonosetron (extemporaneous or FDC) as a single dose (up to 600 mg) to 431 subjects and as a daily dose for 7 days (up to 450 mg daily for 7 days) to 26 subjects has shown to be generally well tolerated. In the Phase II studies, type, frequency, and intensity of adverse events (AEs) were comparable across treatment groups receiving oral netupitant at the doses of 100, 200 and 300 mg in combination with palonosetron. Netupitant daily doses up to 200 mg administered for 8 consecutive weeks did not raise any safety concern in another Phase II study.
ECG data and QT intervals collected up to now suggest a low risk for QT prolongation. Frequency of AEs, changes in clinical laboratory parameters, vital signs and 12-lead ECGs do not suggest any substantial increase in risk when netupitant is combined with palonosetron (4).

Single ascending doses of fosnetupitant chloride hydrochloride ranging from 19.5 mg to 390 mg were well tolerated after administration of IV infusion solutions at the concentration of 2.6 mg/mL over 30 min to healthy male and female subjects (5). The safety results were in line

with the current knowledge about the safety of netupitant. The most frequently reported TEAEs assessed as drug-related were headache, constipation, infusion site thrombosis, abdominal pain, fatigue, and dizziness. The proportion of subjects with drug-related TEAEs did not increase with ascending fosnetupitant chloride hydrochloride doses.
The satisfactory local tolerability profile of IV fosnetupitant chloride hydrochloride was confirmed by thorough vascular surveillance.
The good safety and tolerability profile of 30 min IV infusions of fosnetupitant at 130 mg, 195 mg and 260 mg doses and infusion solution concentrations of 2.6 mg/mL, 3.9 mg/mL and 5.2 mg/mL was confirmed in a second study in healthy subjects concomitantly administered with dexamethasone (5).

Two clinical studies have been completed with the IV fosnetupitant 235mg/palonosetron 0.25 mg combination.
Overall, more than 400 male and female cancer patients received the IV NEPA FDC combination in more than 1300 chemotherapy cycles from two studies in cancer patients: a phase 3 safety study following repeated chemotherapy cycles in cancer patients receiving HEC (mainly cisplatin) (4), and a phase 3b safety study in women with breast cancer receiving repeated AC-chemotherapy cycles (4).
Results obtained from these studies confirmed the good local and systemic tolerability profile of the IV NEPA FDC, similar to that of the oral Akynzeo® formulation.

8.5 Study rationale

IV Akynzeo® (fosnetupitant 235 mg/palonosetron 0.25 mg) has been developed and registered as lyophilized powder for injection in US in April 2018 and in Europe in March 2020.

Helsinn also developed a liquid pharmaceutical form as a solution for infusion, which has been approved by FDA in May 2020, by EMA in November 2021 and by Swissmedic in September 2022.

The registered Akynzeo® liquid formulation for IV administration is to be diluted with 30 mL of either glucose 5% solution for injection, or 0.9% saline solution for injection, up to a final volume of 50 mL and administered during 30 min infusion starting approximately 30 min before chemotherapy.

With the aim to give the possibility of using IV fosnetupitant with any available 5-HT_3 RA, resulting therefore in more flexible therapeutic options for prescribers, the Sponsor is developing a liquid formulation for infusion, containing exclusively fosnetupitant 235 mg free base, the same amount as in the IV fosnetupitant/palonosetron combination product.
In consideration of possible shortages of dilution solutions for IV administrations, and to facilitate and improve the use of the product, the Sponsor focuses on the development of a ready to use solution, not requiring additional dilutions, and possibly to be administered as a bolus injection instead of a 30 min infusion.

The administration of Akynzeo® liquid formulation without further dilution with 30 mL of diluent is not expected to have safety or tolerability issues since the injected quantities of both fosnetupitant and palonosetron at the infusion site remain unchanged. Moreover, it should be noted that a change in excipients quantity in the formulation at the site of injection is considered

to have no impact on tolerability, since local tolerability at the infusion site can be affected by excipients only when they are interacting physically and chemically with the active substance to keep it in solution or to mask its characteristic (typically when solvents, co-solvent or surfactants are present in the formulation) (6).

Therefore, the present study aims at assessing the safety and PK profile of a 235 mg fosnetupitant ready to use solution for IV bolus administration. From a clinical point of view, the present study will also support fosnetupitant 235 mg IV to be administered as a single agent in combination with other antiemetic agents for the proposed indication of prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.
In addition, the PK profile of fosnetupitant and netupitant with its main metabolites will be investigated also after a 30-min infusion of the registered Akynzeo® liquid formulation, administered undiluted as a 20-mL volume.

8.6 Risks and benefits

Healthy male and female subjects will take part in the study. In Part A, each subject will receive one single injection of 20 mL of IV fosnetupitant at decreasing infusion durations from 30 min to 15, 5 and 2 min in the respective study cohort or a 30-min infusion of the 20 mL (undiluted) IV Akynzeo FDC (Rα treatment limited to 10 subjects in cohort 1). Different subjects will be treated in each cohort. In Part B, following a 20-mL saline solution for infusion administered as placebo at the infusion duration established in study Part A, new subjects will receive in 2 study periods a single administration of the 20 mL IV fosnetupitant solution (T, test treatment) at the infusion duration established in study Part A and a single 20 mL IV Akynzeo infusion diluted to 50 mL and administered in 30 min (R, reference treatment), according to a cross-over design.

Blood sampling with cannula insertion and repeated venipuncture may cause minor discomfort. The risks associated with blood draws include pain, bleeding and bruising.

No specific benefits for the healthy subjects participating in the current study are foreseen except for the medical screening. Subject remuneration will be paid to each participating subject after study completion. The remuneration covers loss of time and any inconvenience caused by the participation in the study.

9 STUDY OBJECTIVES

9.1 Objectives of Part A

9.1.1 Primary objective

The primary objective of the study Part A is to define the shortest safe and tolerable duration of IV injection of T among 4 durations tested in decreasing order: 30, 15, 5 and 2 min, respectively. The selected shortest (safe and tolerable) injection duration determined in Part A will be considered for testing in study Part B.

9.1.2 Secondary objective

The secondary objectives of the study Part A are:

- to characterize the pharmacokinetic (PK) profile in plasma of fosnetupitant, netupitant and netupitant metabolites M1, M2 and M3 after injection of T administered at the relevant injection duration and after injection of undiluted R (defined as Rα).
- to determine the safety and tolerability of T administered at the relevant injection duration.

9.2 Objectives of Part B

9.2.1 Primary objective

The primary objective of the study Part B is to investigate the exposure equivalence of T, at the shortest injection duration defined as safe in Part A, and R, administered as a 30 min diluted infusion. The equivalence in exposure will be estimated in terms of extent of exposure to netupitant ($AUC_{0-\infty}$ and AUC_{0-t}).

9.2.2 Secondary objectives

The secondary objectives of the study Part B are:

- To characterize the PK profile in plasma of fosnetupitant, netupitant and netupitant metabolites M1, M2 and M3 after administration of T at the shortest injection duration defined as safe in Part A and R, administered as 30 min diluted infusion.
- To confirm the safety and tolerability of T administered at the shortest injection duration defined as safe in Part A in comparison to R, administered as a 30 min diluted infusion.
- To assess the effect of T on ECG parameters (HR, QT, QTcF, QTcB, PR and QRS intervals).
- To assess the effects of the administration of fosnetupitant on the QT interval in the shortest infusion time (defined in Part A) compared to placebo, in male and female healthy subjects.

10 CLINICAL SUPPLIES

10.1 Treatment

The study will be divided into 2 parts. In study Part A, 40 subjects will receive one single IV dose of T as a single injection with a varying duration according to the admittance cohort, and 10 subjects will receive one single IV dose of undiluted R (defined as Rα) as one single 30-min IV infusion.

In study Part B, each subject (subjects different from those included in Part A) will undergo a 2-period, randomized cross-over study, and will receive one single IV dose of T as a single injection in one period (at the injection duration selected in Part A) and one single 30-min IV infusion of R diluted to 50 mL, in the other period. A wash-out period of at least 28 days will elapse between the two consecutive administrations. All the subjects will also receive one single IV dose of P (placebo, as 0.9% sodium chloride solution for infusion) in period 1, before receiving the first assigned active treatment.

10.1.1 Description of products

The analytical certificates will be supplied with the investigational medicinal products (IMPs).

10.1.1.1 Test product

TEST (T)	
IMP	Fosnetupitant free base 235 mg ready to use solution for intravenous administration
Manufacturer of finished product	Patheon Italia S.p.A., Italy (GMP compliant)
Pharmaceutical form	Injectable solution (20 mL)
Dose	Fosnetupitant 235 mg (corresponding to 260 mg of the chloride hydrochloride salt)
Administration route	IV

10.1.1.2 Reference product

REFERENCE (R)	
IMP	IV Akynzeo (235 mg fosnetupitant/0.25 mg palonosetron) in 20 mL injectable solution
Manufacturer of finished product	Baxter Oncology GmbH, Germany (GMP compliant)
Marketing authorization holder	Helsinn Birex Pharmaceuticals Ltd., Ireland
Pharmaceutical form	Injectable solution (20 mL)
Dose	Fosnetupitant 235 mg (corresponding to 260 mg of the chloride hydrochloride salt)/palonosetron 0.25 mg
Administration route	IV

10.1.1.3 Test product placebo

PLACEBO (P)	
IMP	0.9% sodium chloride injection solution, ready to use solution for intravenous administration
Manufacturer of finished product	Commercially available product purchased from the market
Pharmaceutical form	Injectable solution (20 mL)
Administration route	IV

10.1.2 Dose regimen

Part A of the study:

In cohort 1, 10 healthy volunteers (HV) will receive a dose of T as a one single 30-min IV infusion and additional 10 subjects will receive a single IV dose of undiluted R (defined as Rα) as a one single 30-min IV infusion, according to a parallel group design. In each of 3 consecutive cohorts (cohorts 2, 3 and 4), 10 healthy volunteers (HV) will receive a single IV dose of T at a predefined infusion duration and will be sequentially treated as 3 subgroups of 3, 3, and 4 subjects, respectively.

A staggered approach with decreasing infusion time duration will be applied, from cohort 1 to cohort 4, to the administration of T, as follows:

Cohort 1: 30 min

Cohort 2: 15 min

Cohort 3: 5 min

Cohort 4: 2 min

At the end of cohort 1 and of each subgroup of cohorts 2, 3 and 4, safety and tolerability results will be evaluated by the Investigator and the study Sponsor Medical Expert. Predefined stopping rules will be considered for deciding about continuing with the next cohort treatment and a shorter injection duration of T (see § 13.2). Predefined stopping rules are applicable for subjects treated with T. After cohort 1, if the injection duration of 30 min proves to be safe and well tolerated, 15 min injection duration will be tested in cohort 2. If the injection duration of 15 min proves to be safe and well-tolerated, 5 min injection duration will be tested in cohort 3. If the injection duration of 5 min proves to be safe and well tolerated, a 2 min injection will be tested in cohort 4. If the safety data obtained from a treated cohort receiving T are considered as not sufficient for taking a decision on the infusion duration de-escalation process, and if additional safety data are deemed necessary to allow such decision to be taken, the study Investigator and the Sponsor Medical Expert may decide to add additional subjects (up to a maximum of 4 subjects per cohort) to the 10 subjects of the treated cohort.

Part B of the study will follow a 2-way, cross-over randomized design and will include 40 subjects.

All the subjects will receive one single IV dose of P (placebo, as 0.9% NaCl solution for infusion) in period 1, at the infusion duration selected in study part A.
Each subject will then receive T followed by R or R followed by T in period 1 and 2 respectively, according to the randomization schedule. The duration of T injection will be the one selected in study Part A, while R (diluted to 50 mL) will be administered in 30 min. A wash-out period of at least 28 days will elapse between the two consecutive administrations of T and R (28-day wash-out between Day 3 of period 1 and Day 1 of period 2).

10.1.2.1 Route and method of administration

T, P, Rα (undiluted R) and R will be administered using a pump at a controlled rate according to the scheduled injection/infusion duration.

For the administration of T or P, the whole volume of 20-mL will be injected.

For the administration of Rα, 20 mL of the undiluted injectable solution will be infused in 30 min (Part A) while for the administration of R, 20 mL of the injectable solution will be first diluted with a saline solution (0.9% NaCl) to a volume of 50 mL and then infused in 30 min (Part B).

The Investigator will check that all subjects receive T or P or Rα or R appropriately.

10.1.3 Investigational product distribution

T, P, Rα and R will be only administered to the subjects enrolled in this study by the Investigator or by his/her deputy and will be exclusively used for the present clinical study.

10.2 Packaging and labeling

The primary packaging will be *20R* type vials for T, P, Rα and R.
Identifiable vials of all 3 products will be supplied in excess of the amount necessary for the study.
The vials will be provided secondary packed in sealed racks. It will be the responsibility of the Phase I Unit Investigator or deputy to collect the correct number of vials for the specific treatment's preparation.
Different colors will be used for labeling in order to easily identify T, P and R vials. Moreover, each vial will carry a unique identification number used for traceability. A "peel-off" removable portion is available on each vial's label; this will be removed from the site Investigator or deputy as soon as the vial is used for treatment preparation and applied on subject's specific source document aimed to track each subject's treatment.
The labeling will report all the information requested according to the Annex 13 to the Good Manufacturing Practice (published by the Commission in "The rules governing medicinal products in the European Community", Volume 4) (7) as follows:

a. Name, address and telephone number of the Sponsor, contract research organization or Investigator (the main contact for information on the product, the clinical study and emergency unblinding)

b. Pharmaceutical dosage form, route of administration, quantity of dosage units, the name and strength

c. The batch and/or code number to identify the contents and packaging operation

d. A study reference code allowing identification of the study, site, Investigator and Sponsor if not given elsewhere

e. The name of the Investigator (if not included in (a) or (d))

f. Directions for use (reference may be made to a leaflet or other explanatory document intended for the study subject or person administering the product)

g. "For clinical study use only" "Caution New Drug, Limited by Federal (or United States) law to investigational use" or similar wording

h. The storage conditions

i. Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity

j. "Keep out of reach of children"

Labels will be in English.

10.3 Storage conditions

The provided IMPs vials for study Parts A and B will be stored at the following conditions: room temperature (i.e., 15-25° C) protected from light at the Phase I Unit.

10.4 Drug accountability

The IMPs will be provided directly to the Investigator by the manufacturer, in excess of the amount necessary for the study conduction in order to have an amount of 30 reserve vials sufficient to perform all of the release tests required in the application or supplemental application.

The diluent and the ancillary material needed for the dilution of R (Part B) will be provided by the CRO.

After receipt of the IMP supply, the Investigator will confirm in writing by signing and dating standard drug accountability forms.

At the end of the study, adequate accountability of the used, unused and partially used supplies of IMPs will be provided to the Sponsor and used and partially used supplies will be destroyed on site, following written Sponsor authorization. The relevant certificate of destruction will be provided to the study Sponsor. At the end of the study, the reserve samples will be kept at the Phase I Unit in compliance with the FDA requirements about retention samples.

11 INVESTIGATIONAL PLAN

11.1 Overall study design

Open label, single dose, two parts (part A and part B), safety and PK phase I study. Study Part B will be conducted according to a randomized cross-over design

11.2 Discussion of design

The study design is based upon that of a previous study of CINVANTI® (aprepitant injectable emulsion) published by Ottoboni *et al*. (8) where it is described that, due to a shortage of small-volume parental solutions, the American Society of Health-System Pharmacists recommended switching the delivery of treatments from infusion to IV push.
The study design is in compliance with the relevant FDA guidance document for industry on bioavailability studies (9).

The selected dose for the fosnetupitant component is 235 mg, corresponding to 260 mg of fosnetupitant chloride hydrochloride, previously shown to be equivalent in exposure (Netupitant AUC) to the netupitant dose present in the oral NEPA FDC (300 mg of netupitant).

The blood sampling times scheduled for the measurement of plasma concentrations of fosnetupitant, netupitant and its metabolites are consistent with the known PK profile of the analytes.

The evaluation of the bioequivalence between T (administered as per infusion duration selected in study Part A) and R will be based on the T/R geometric mean ratio of netupitant AUC_{0-t} and $AUC_{0-\infty}$ and their relevant 90% confidence interval (CI). The T/R geometric mean ratio and 90% CI of AUC_{0-120} are calculated to compare the exposures after T and R in the time interval 0-120 h in which acute and delayed chemotherapy induced emesis may occur. The T/R geometric mean ratio and 90% CI of netupitant C_{max} will also be calculated but not considered for the bioequivalence evaluation because C_{max} is expected to be higher after IV bolus administration (T treatment) as compared to the 30-min IV infusion of diluted R treatment.
The assessment of T and R bioequivalence will be conducted on netupitant. The prodrug fosnetupitant is known to be promptly transformed into netupitant after the administration. Netupitant is the active species endowed with antiemetic efficacy in the delayed phase of emesis, defined as the period of time from 24 h after start of chemotherapy treatment onwards, up to 120 h after start of chemotherapy. Thirty (30) min after the end of the 30-min IV infusion in cancer patients, fosnetupitant mean plasma concentration was <1% of C_{max}. The prodrug was detectable until 2 to 4 h after the start of infusion (mean t_{last} 3.13 h). Netupitant peak concentrations were reached at the end of fosnetupitant infusion and netupitant exposure was appreciated for several days after IV administration with MRT and $t_{1/2}$ values of 162.6 h and 143.7 h, respectively (10).

12 STUDY POPULATION

12.1 Target population

Male and female adult healthy volunteers aged between 18 and 55 years old.

12.2 Inclusion criteria

To be enrolled in this study, subjects must fulfil all these criteria:

1. *Informed consent*: signed written informed consent before inclusion in the study
2. *Sex and Age*: healthy men/women volunteers, 18-55 years old (inclusive)
3. *Body Mass Index (BMI)*: 18.5-30 kg/m^2 inclusive
4. *Vital signs*: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, pulse rate 50-99 bpm, measured after 5 min at rest in the sitting position
5. *Full comprehension*: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the investigator and to comply with the requirements of the entire study
6. *Contraception and fertility (women only):* women of childbearing potential defined as a non-menopausal woman who has not had a bilateral oophorectomy or medically documented ovarian failure and/or at risk for pregnancy must agree, signing the informed consent form, to use a highly effective method of contraception throughout the study and to continue for 14 days after the last dose of the study treatment. Highly effective contraceptive measures include:
    a. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit.
    b. A non-hormonal intrauterine device [IUD] for at least 2 months before the screening visit
    c. A sterile or vasectomized sexual partner
    d. True (long-term) heterosexual abstinence, defined as refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject, while periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), lactational amenorrhea and withdrawal are not acceptable.

    Women of non-child-bearing potential or in post-menopausal status defined as such when there is either:

    a. 12 months of spontaneous amenorrhea or
    b. 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or
    c. 6 weeks documented postsurgical bilateral oophorectomy with or without hysterectomy

    will be admitted.
    For all women, pregnancy test result must be negative at screening and admission (Day -1).

7. *Contraception (men only)*: men will either be sterile or agree to use one of the following approved methods of contraception from the first study drug administration until at least 14 days after the last administration, also in case their partner is currently pregnant:
    a. A male condom with spermicide
    b. A sterile sexual partner or a partner in post-menopausal status for at least one year
    c. Use by the female sexual partner of an IUD, a female condom with spermicide, a contraceptive sponge with spermicide, a diaphragm with spermicide, a cervical cap with spermicide, or hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit

    Men must accept to inform their partners of the participation in the clinical study. Furthermore, they will not donate sperm from the date of the informed consent form's signature, throughout the study, and for at least 14 days after the last dose of the study treatment. These requirements are based upon the availability and results of reproductive toxicity data.

12.3 Exclusion criteria

Subjects meeting any of these criteria will not be enrolled in the study:

1. *12-leads Electrocardiogram (ECG) (supine position)*: clinically significant abnormalities at screening. With regards to QTc, the following will be considered as exclusion criterion: mean corrected QT (QTcF) > 450 ms. HR < 50 or > 99 bpm. PR < 100 or >220 ms. QRS > 120 ms. Relevantly abnormal T-wave patterns
2. *Physical examination findings*: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. *Laboratory analyses*: clinically significant abnormal laboratory values at screening, indicative of physical illness or suggesting the subject's exclusion, in his/her best interest
4. *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study
5. *Diseases*: significant history, in the opinion of the Investigator, of renal, hepatic, gastrointestinal, cardiovascular (in particular, heart failure, hypokalemia, family history of Long QT Syndrome, 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. *Medications*: medications, including over the counter (OTC) medications and herbal remedies in the 2 weeks before the first visit of the study. Hormonal contraceptives for women are allowed
7. *CYP3A4 inducers and inhibitors:* use of any inducer or inhibitor of CYP3A4 enzymes (drugs, food, herbal remedies) in the 28 days or in the 7 days, respectively, before the planned first study drug administration and during the whole study
8. *Investigative drug studies*: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first

calendar day of the month that follows the last visit of the previous study and the first day of the present study

9. *Blood donation or significant blood loss*: blood donations or significant blood loss in the 3 months before the first visit of this study
10. *Drug, alcohol, caffeine, tobacco*: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2020-2025 (11)], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
11. *Drug test*: positive result at the urine drug screening test at screening or Day -1
12. *Alcohol test*: positive salivary alcohol test at Day -1
13. *Diet*: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before screening; vegetarians
14. *Pregnancy (women only)*: positive or missing pregnancy test at screening or Day -1, pregnant or lactating women
15. *Netupitant studies*: enrolment in a previous study of netupitant or fosnetupitant (alone or in combination with palonosetron)

12.3.1 Not allowed treatments

No medication, including OTC and herbal remedies, will be allowed in the 2 weeks before the first visit of the study (Screening - Visit 1) and during the whole study duration. In particular, the use of CYP3A4 inducers or CYP3A4 inhibitors (drugs, food, herbs) in the 28 days or in the 7 days, respectively, before the 1st study treatment intake on Day 1 will not be allowed.

Paracetamol will be allowed as therapeutic countermeasure for certain types of AEs according to the Investigator's opinion. Hormonal contraceptives will be allowed.

The intake of any other medication will be reported as a protocol deviation. However, it will lead to subject's discontinuation from the study only if the Investigator, together with the Sponsor, considers the medication as being able to affect the study assessments or outcome.

12.4 Use of contraceptive methods

In case of men or women of childbearing potential, the Investigator, in consultation with the subject, will select the appropriate method/methods of contraception for the individual according to the list of contraception methods of inclusion criteria 6 and 7, and instruct the subject or a screened man referring to his partner in their consistent and correct use. Highly effective contraceptive measures include those listed in inclusion criteria 6 and 7.
Moreover, men will not donate sperm from the date of the informed consent form's signature, throughout the study, and for at least 14 days after the last dose of the study treatment.
At screening and at each study visit, the Investigator will instruct subjects on the need to use contraception throughout the study and to continue for 14 days after the last dose of assigned treatment. In addition, the Investigator will instruct the subjects to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected.

13 STUDY SCHEDULE

The schedule of the study is summarized in Table 4.1 for study Part A and in Table 4.2 for study Part B.

13.1 Study visits and procedures

Each subject taking part in study Part A will undergo 4 visits, while each subject participating in Part B will undergo 21 visits.

Study **Part A** foresees, after the screening process, a confinement of approximately one and a half days at the Phase I Unit and one ambulatory visit (V4) 7 days post-dose. The maximum study duration for study part A will be 28 days, including the screening period.
Study **Part B** foresees 2 periods separated by a wash-out interval of at least 28 days between the day of T and the day of R treatment administration. After a confinement of approximately 2 and a half days at the Phase I Unit for the treatment with P, the subjects will remain confined for period 1 for approximately 2 further days. Period 2 will consist in a confinement of approximately 3 days at the Phase I Unit. In each period, the confinement will be followed by 8 ambulatory visits, the last of which will be the final visit (Visit 21). The maximum study duration for study Part B will be 62 days, including the screening period (Days -21 to -2) and assuming a 28-day wash-out period between active treatment (T or R) administration days (Day 3 of period 1 and Day 1 of period 2).

The first subject first visit (FSFV) is defined as the 1st screening visit performed at the Phase I Unit for study part A by the 1st screened subject. The last subject last visit (LSLV) is defined as the last visit performed at the Phase I Unit by the last subject in study part B, i.e., the last visit foreseen by the study protocol, independently of the fact that the subject is a completer or a withdrawn subject.

The following parts, phases, visits and procedures will be performed:

- **Part A**
- **Screening phase**
  - Screening – visit 1: between Day -21 and Day -2
  - Visit 2: Day -1
- **Interventional phase**
  - Visit 3: Days 1-2
- **Final phase**
  - Visit 4: Day 7: Final visit or Early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an ETV.
- **Part B**
- **Screening phase**

- Screening – visit 1: between Day -21 and Day -2
- Period 1 – visit 2: Day -1

➢ **Interventional phase**

- Period 1 – visit 3: Days 1-5
- Period 1 – visit 4: Day 6
- Period 1 – visit 5: Day 7
- Period 1 – visit 6: Day 8
- Period 1 – visit 7: Day 9
- Period 1 – visit 8: Day 10
- Period 1 – visit 9: Day 11
- Period 1 – visit 10: Day 12
- Period 1 – visit 11: Day 13
- Wash-out interval of at least 28 days between the 2 administration days of T and R (Day 3 of period 1 and Day 1 of period 2)
- Period 2 – visit 12: Day -1
- Period 2 – visit 13: Days 1-3
- Period 2 – visit 14: Day 4
- Period 2 – visit 15: Day 5
- Period 2 – visit 16: Day 6
- Period 2 – visit 17: Day 7
- Period 2 – visit 18: Day 8
- Period 2 – visit 19: Day 9
- Period 2 – visit 20: Day 10

➢ **Final phase**

- Period 2 – visit 21: Day 11: Final visit or Early termination visit (ETV). In case of early discontinuation, discontinued subjects will undergo an ETV.

Table 13.1.1 Study procedures of Part A

	Day	Procedures/Assessments	Notes
Screening – visit 1	*From Day -21 to Day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number assignment (as S001, S002, etc.) (§ 20.2) ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, body mass index, vital signs, physical abnormalities) (§ 14.1) ➢ Triplicate 12-lead ECG recording (§14.3.1) ➢ Laboratory analyses: hematology, blood chemistry, urinalysis and virology ➢ Serum pregnancy test (women only) ➢ Urine multi-drug screening test ➢ AE recording ➢ Inclusion/exclusion criteria evaluation	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the Phase I Unit source document only and will not be transferred to the Sponsor
Visit 2	*Day -1*	➢ Short physical examination (only if screening physical examination performed more than 7 days before Day -1) (§ 14.1) ➢ Recording of concomitant medications ➢ Salivary alcohol test ➢ Urine pregnancy test (women only) ➢ Urine multi-drug screening test ➢ Body weight (§ 14.1) ➢ Vital signs measurement (§ 14.2) ➢ AE recording ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment ➢ Subject study number assignment (as 001, 002, etc.) (§ 20.2)	Arrival at the Phase I Unit in the evening Confinement until the morning of Day 2 Standardized low-fat dinner Fasting for 10 h (overnight)
Visit 3	*Day 1*	➢ T or Rα treatment ➢ Vital signs measurement (§ 14.2) ➢ Triplicate 12-lead ECG recording (§14.3.1) ➢ Blood sample collection for PK analysis (§ 14.5.1) ➢ Recording of concomitant medications ➢ AE recording	Standardized lunch at about 13:00 (5 h post-dose) Standardized dinner at about 20:00 (12 h post-dose)
	Day 2	➢ Vital signs measurement (§ 14.2) ➢ Triplicate 12-lead ECG recording (§14.3.1) ➢ Blood sample collection for PK analysis (§ 14.5.1) ➢ Recording of concomitant medications ➢ Short physical examination upon discharge (§ 14.1) ➢ AE recording	Discharge from the Phase I Unit in the morning after the 24-h post-dose blood sample collection, ECG recording and vital signs check

	Day	Procedures/Assessments	Notes
Visit 4 - Final Visit/ETV	*Day 7 / at ETV in case of discontinuation*	➢ Full physical examination (body weight and physical abnormalities) (§ 14.1) ➢ Recording of concomitant medications ➢ Vital signs measurement (§ 14.2) ➢ Triplicate 12-lead ECG recording (§14.3.1) ➢ Urine pregnancy test (women only) ➢ Laboratory analyses as at screening, except for virology ➢ AE recording In case of clinically significant results at the final visit, the subjects will be followed-up by the Investigator until the normalization of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions

Table 13.1.2 Study procedures of Part B

	Day	Procedures/Assessments	Notes
Screening – visit 1	*From Day -21 to Day -2*	➢ Explanation to the subject of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number assignment (as S101, S102, etc.) (§ 20.2) ➢ Demographic data and lifestyle recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (body weight, height, body mass index, vital signs, physical abnormalities) (§ 14.1) ➢ Triplicate 12-lead ECG recording (§14.3.1) ➢ Laboratory analyses: hematology, blood chemistry, urinalysis and virology ➢ Serum pregnancy test (women only) ➢ Urine multi-drug screening test ➢ AE recording ➢ Inclusion/exclusion criteria evaluation	*Note:* The first two letters of the surname followed by the first two letters of the first name will be used in the Phase I Unit source document only and will not be transferred to the Sponsor
Visit 2	*Day -1*	➢ Short physical examination (only if screening physical examination performed more than 7 days before Day -1) (§ 14.1) ➢ Recording of concomitant medications ➢ Salivary alcohol test ➢ Urine multi-drug screening test ➢ Urine pregnancy test (women only) ➢ Body weight (§ 14.1) ➢ AE recording ➢ Inclusion/exclusion criteria evaluation ➢ Eligibility evaluation ➢ Enrolment and randomization ➢ Subject randomization number assignment (as 101, 102, etc.) (§ 20.2)	Arrival at the Phase I Unit in the evening Confinement until the morning of Day 5 Standardized low-fat dinner Fasting for 10 h (overnight)

	Day	Procedures/Assessments	Notes
Visit 3	*Day 1*	➢ P treatment ➢ Vital signs measurement (§ 14.2) ➢ Continuous 12-lead ECG recording (§ **Error! Reference source not found.**) ➢ Triplicate 12-lead ECG recording (§ 14.3.1) ➢ Recording of concomitant medications ➢ AE recording	Standardized lunch at about 13:00 (5 h post-dose) Standardized dinner at about 20:00 (12 h post-dose)
	Day 2	➢ Vital signs measurement (§ 14.2) ➢ Continuous 12-lead ECG recording (§ **Error! Reference source not found.**) ➢ Triplicate 12-lead ECG recording (§ 14.3.1) ➢ Recording of concomitant medications ➢ AE recording	Standardized breakfast, lunch and low-fat dinner at about 08:00, 13:00 and 20:00 and then fasting for 10 h (overnight)
	Day 3	➢ T or R treatment ➢ Vital signs measurement (§ 14.2) ➢ Continuous 12-lead ECG recording (§ **Error! Reference source not found.**) ➢ Triplicate 12-lead ECG recording (§ 14.3.1) ➢ Recording of concomitant medications ➢ Blood sample collection for PK analysis (§ 14.5.1) ➢ AE recording	Standardized lunch at about 13:00 (5 h post-dose) Standardized dinner at about 20:00 (12 h post-dose)
	Day 4	➢ Vital signs measurement (§ 14.2) ➢ Continuous 12-lead ECG recording (§ **Error! Reference source not found.**) ➢ Triplicate 12-lead ECG recording (§ 14.3.1) ➢ Recording of concomitant medications ➢ Blood sample collection for PK analysis (§ 14.5.1) ➢ AE recording	Standardized breakfast, lunch and dinner at about 08:00, 13:00 and 20:00
	Day 5	➢ Vital signs measurement (§ 14.2) ➢ Continuous 12-lead ECG recording (§ **Error! Reference source not found.**) ➢ Triplicate 12-lead ECG recording (§ 14.3.1) ➢ Recording of concomitant medications ➢ Blood sample collection for PK analysis (§ 14.5.1) ➢ AE recording	Discharge from the Phase I Unit in the morning after the 48-h post-dose blood sample collection, ECG recording and vital signs check
Visit 4	*Day 6*	➢ Blood sample collection for PK analysis: 72 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	Ambulatory visit. Arrival at the Phase I Unit in the morning.
Visit 5	*Day 7*	➢ Blood sample collection for PK analysis: 96 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 4

	Day	Procedures/Assessments	Notes
Visit 6	*Day 8*	➢ Blood sample collection for PK analysis: 120 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 4
Visit 7	*Day 9*	➢ Blood sample collection for PK analysis: 144 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 4
Visit 8	*Day 10*	➢ Blood sample collection for PK analysis: 168 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 4
Visit 9	*Day 11*	➢ Blood sample collection for PK analysis: 192 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 4
Visit 10	*Day 12*	➢ Blood sample collection for PK analysis: 216 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 4
Visit 11	*Day 13*	➢ Blood sample collection for PK analysis: 240 h post-dose ➢ Recording of concomitant medications ➢ Short physical examination (§ 14.1) ➢ Laboratory analyses as at screening, with the exception of virology ➢ Vital signs measurement (§ 14.2) ➢ Triplicate 12-lead ECG recording (§ 14.3.1) ➢ Urine pregnancy test (women only) ➢ AE recording	As visit 4
Wash-out	*At least 28 days*	A wash-out interval of at least 28 days will elapse between the two administrations of active treatment (T and R) of the two study periods (Day 3 of period 1 and Day 1 of period 2)	
Visit 12	*Day -1*	➢ Short physical examination (§ 14.1) ➢ Recording of concomitant medications ➢ Salivary alcohol test ➢ Urine multi-drug screening test ➢ Urine pregnancy test (women only) ➢ Body weight (§ 14.1) ➢ Laboratory analyses as at screening, except for virology ➢ AE recording	As visit 2

	Day	Procedures/Assessments	Notes
Visit 13	*Days 1-3*	As Days 3-5 of visit 3. T or R treatment according to the randomization list and cross-over design	As Days 3-5 of visit 3
Visit 14	*Day 4*	➢ Blood sample collection for PK analysis: 72 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	Ambulatory visit. Arrival at the Phase I Unit in the morning.
Visit 15	*Day 5*	➢ Blood sample collection for PK analysis: 96 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 14
Visit 16	*Day 6*	➢ Blood sample collection for PK analysis: 120 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 14
Visit 17	*Day 7*	➢ Blood sample collection for PK analysis: 144 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 14
Visit 18	*Day 8*	➢ Blood sample collection for PK analysis: 168 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 14
Visit 19	*Day 9*	➢ Blood sample collection for PK analysis: 192 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 14
Visit 20	*Day 10*	➢ Blood sample collection for PK analysis: 216 h post-dose ➢ Vital signs measurement (§ 14.2) ➢ Recording of concomitant medications ➢ AE recording	As visit 14

	Day	Procedures/Assessments	Notes
Visit 21 - Final Visit/ETV	*Day 11 of period 2 / at ETV in case of discontinuation*	➢ Blood sample collection for PK analysis: 240 h post-dose ➢ Laboratory analyses as at screening, except for virology ➢ Vital signs measurement (§ 14.2) ➢ Triplicate 12-lead ECG recording (§14.3.1) ➢ Urine pregnancy test (women only) ➢ Full physical examination (body weight and physical abnormalities) (§ 14.1) ➢ Recording of concomitant medications ➢ AE recording In case of clinically significant results at the final visit, the subjects will be followed-up by the Investigator until the normalization of the concerned clinical parameter(s)	Upon leaving, the subjects will be instructed to contact immediately the Investigator in case of occurrence of any adverse reactions

13.2 Decisional process for escalation to next administration duration

All TEAEs will be recorded in the CRF. TEAEs will be assessed by the Investigator with focus on general safety and local tolerability (i.e., any TEAEs appearing after start of injection and interesting the injection arm).

Following all planned subject's safety assessments and before subject's discharge, the Investigator will evaluate the reported TEAEs.

13.2.1 Decisional process for treatment of subjects within the cohorts

Subjects belonging to cohort 2, 3 and 4 will be sequentially treated as 3 subgroups of 3, 3 and 4 subjects respectively, in each cohort.
Following the treatment of the first 3 subjects in the cohort, the collected safety parameters will be carefully assessed by the Investigator. In particular, the local tolerability will be evaluated in view of confirming the treatment of the next subgroup of 3 subjects in the same cohort. If deemed necessary, the study Investigator will contact the Sponsor Medical Expert and seek advice.
The same process will be repeated following the second subgroup of 3 subjects for confirming the treatment of the last 4 subjects of the cohort.

13.2.2 Decisional process for escalation to next administration duration

Following the completion of each cohort, the Sponsor Medical Expert will be provided with a summary of the observed tolerability, detailing each TEAE reported up to 60 min after the end of infusion of T and up to subject's discharge on Day 2. The Investigator will provide his assessments on severity and relationship to T. The Investigator will also provide a conclusion on the systemic and local tolerability related to the administration duration of T tested in the cohort, including his suggestion whether to consider safe to proceed with treating the next cohort of subjects with the next predefined infusion duration of T.

If the safety data obtained from a T treated cohort are considered as not sufficient for taking a decision on the infusion duration de-escalation process, and if additional safety data are deemed necessary to allow such decision to be taken, the study Investigator and the Sponsor Medical Expert may decide to add additional subjects (up to a maximum of 4 subjects per cohort) to the 10 subjects of the treated cohort.

The Sponsor Medical Expert will confirm the Sponsor's agreement to proceed or not with the treatment of the next planned subjects' cohort / injection duration.

Study Part A will be stopped if any of the following criteria is met:

1. Any serious adverse event (SAE) assessed as at least possibly related to T experienced within 60 min after the end of T injection 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 with both AEs judged at least as possibly related to T and of severe intensity, within 60 min after the end of T injection.
3. Any AE coded with the same PT occurring to 3 (or more) subjects of the same cohort with the AEs judged at least as possibly related to T and of moderate intensity, within 60 min after the end of T injection.

At the end of study Part A, the Sponsor will take a final decision whether to proceed with study Part B with the resulting shortest injection duration considered as adequate in terms of safety determined in study Part A.

The shortest injection duration selected based on the safety and tolerability results of **Part A,** will be applied in **Part B.**

13.3 Diet and lifestyle

During the subjects' confinement at the Phase I Unit, they will not take any food or drinks (except water) for about 10 h (i.e., overnight) before P, T or R. Water will be allowed as desired, except for 1 h before and 1 h after P, T or R administration start. In order to maintain an adequate hydration, the subjects will be encouraged to drink at least 180 mL of still mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.

On Day 1 of Part A and B and on Day 3 of period 1 (Part B), the subjects will remain fasted until 5 h after the start of injection/infusion. Standardized lunch and dinner will be served at approximately 5 h and 12 h after the start of injection/infusion.

On Day -1 of each study part and period, a standardized low-fat dinner will be served.

One cup of coffee or tea will be allowed after each meal only; any other coffee, tea or food containing xanthines (i.e., coke, energy drinks, chocolate, etc.), alcohol and grapefruit will be forbidden during confinement. In particular, grapefruit and any other food or beverage known to interfere with cytochrome P450 will be forbidden for 7 days (168 h) before the first study treatment administration until the end of the study.

During confinements, smoking will be forbidden.
During confinement, routine ambulant daily activities will be strongly recommended.

13.3.1 Restrictions

In Part A, the subjects will be confined from the evening preceding T or Rα (undiluted R) treatment (study Day -1) until the morning of Day 2. In Part B, the subjects will be confined from the evening preceding P treatment (study Day -1) until the morning of Day 5 in period 1 and from the evening preceding T or R treatment (study Day -1) until the morning of Day 3 in period 2. All other study visits will be ambulatory.
During confinement, hazardous, strenuous or athletic activities will not be permitted.

14 DESCRIPTION OF SPECIFIC PROCEDURES

NB: the PK sampling times are indicated from the **start** of infusion, while the timing of safety measures is indicated from the **end** of infusion.

14.1 Physical examination

Full physical examinations will be performed at the screening and final visit / ETV. Body weight (BW) will be also recorded. The following apparatuses/systems will be checked:

- General appearance
- Chest/respiratory
- Gastrointestinal
- Head, eyes, ears, nose and throat
- Heart/cardiovascular
- Lymph nodes
- Metabolic/endocrine
- Musculoskeletal/extremities
- Neck (including thyroid)
- Neurological/psychiatric
- Skin/dermatologic

Any abnormalities will be recorded.

Short physical examinations will be performed upon confinements (with measurement of BW), discharges and/or end of periods (without measurement of BW) (Table 13.1.2). Information about the physical examination will be recorded by the Investigator. The following apparatuses/systems will be checked:

- General appearance
- Chest/respiratory
- Heart/cardiovascular
- Lymph nodes
- Neurologic/psychiatric
- Skin/dermatologic

Any abnormalities will be recorded.

Significant findings/illnesses, reported after the start of the study and that meet the definition of an AE (see § 18), will be recorded in the subject source documents.

Date of the physical examination, overall Investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs.

Subjects will be weighed (kg) lightly clothed without shoes. Height will be measured at screening only and BMI will be recorded. BMI will be calculated as weight [kg]/(height [m] x height [m]).

Physical examinations will be performed at the following times during the 2 study parts:

Part A

- Screening visit (Full physical examination)
- Upon confinement on Day -1 only if screening performed more than 7 days before (Short physical examination). BW will be measured on both occasions
- Upon discharge on Day 2 (Short physical examination)
- Final visit/ETV (Full physical examination)

Part B

- Screening visit (Full Physical Examination)
- Upon confinement on Day -1 of period 2 (Short physical examination). Also in period 1, only if screening performed more than 7 days before (Short physical examination). BW will be measured in both periods
- At the end of period 1 (Day 13) (Short physical examination)
- Final visit/ETV (Full physical examination)

14.2 Vital signs

Subjects' blood pressure (BP) and pulse rate will be measured by the Investigator or his/her deputy after 5 min at rest in sitting position.

Measurements will be performed at the following times during the 2 study parts:

Part A

- Screening visit
- Upon confinement on Day -1
- On Day 1, at pre-dose, at the end of the injection and 1, 2 and 4 h after the end of the injection
- Upon discharge on Day 2 (24 h after the end of the injection)
- Final visit/ETV

Part B

- Screening visit
- On Day 1 of each period and on Day 3 of period 1, at pre-dose, at the end of the injection/infusion and 1, 2, 4 and 24 h after the end of the injection/infusion
- Upon discharge on Day 5 of period 1 and on Day 3 of period 2 (48 h after the end of the injection/infusion)
- On Days 6, 7, 8, 9, 10, 11, 12, 13 of period 1 and on Days 6, 7, 8, 9, 10, 11 of period 2 (Ambulatory visits) (in period 2, coinciding with the final visit measurement)
- ETV

Actual measurement times for each subject will be recorded in the individual case report forms (CRFs). The actual times should not exceed the recommended tolerance ranges presented in the following table. Any deviation outside the recommended ranges will be verified through Data Clarification Forms and, if confirmed, will be reported as protocol deviation.

Table 14.2.1 Tolerance ranges for the measurements of vital signs

Scheduled time	Tolerance range
Pre-dose (0) of Day 1	2 h before the start of the injection/infusion
At the end of injection/infusion	+10 min
1, 2 h	+10 min
4 h	±1 h
24, 48 h	± 2 h

14.3 12-lead ECGs

14.3.1 12-lead ECGs recorded at the Phase I Unit for immediate safety evaluation

Triplicate 12-lead ECGs will be recorded in supine position after 5 min at rest by the Investigator or his/her deputy for immediate safety evaluations.

Triplicate 12-lead ECGs will be recorded at the following times during the 2 study parts:

Part A

- Screening visit
- On Day 1, at pre-dose, at the end of the injection and 1, 2 and 4 h after the end of the injection
- Upon discharge on Day 2 (24 h after the end of the injection)
- On Day 7, the final visit
- ETV

Part B

- Screening visit
- On Day 1 period 1, at pre-dose and 1 and 2 h after the end of the infusion
- On Day 2 of period 1 (24 h after the end of the infusion)
- On Day 3 of period 1 and on Day 1 of period 2, at pre-dose and 1 and 2 and 24 h after the end of the injection/infusion
- On Day 13 of period 1 and Day 11 of period 2 (in period 2, coinciding with the final visit measurement)
- ETV

Triplicate 12-lead ECG parameters and abnormalities will be recorded in the individual CRFs.

14.3.2 Continuous 12-lead ECG

In Part B, on each dosing day, a continuous 12-lead ECG will be recorded and discrete triplicate recordings will be extracted from the continuous Holter ECG monitoring for the data analysis.

Continuous 12-lead ECG will be recorded:

- On Day 1 period 1, from 1 h before to 48 h after the end of the infusion. In addition, discrete triplicate 12-lead ECGs will be extracted 3 times within 1 h before the start of infusion and at the end of the infusion and 0.5, 1, 2, 4 and 24 h after the end of the infusion
- On Day 3 of period 1 and on Day 1 of period 2, from shortly before the injection/infusion start to 48 h after the end of the infusion/infusion. In addition, discrete triplicate 12-lead ECGs will be extracted at pre-dose 3 times within 1 h before the start of the injection/infusion and at the end of the injection/infusion and 0.5, 1, 2, 4, 24 and 48 h after the end of the injection/infusion

ECG continuous recording will be performed using appropriate continuous 12-lead recording devices with the capacity for digital signal processing, adequately serviced and calibrated. For the ECG monitoring, the operator will always apply the same technique for skin preparation, lead placement and time of recording. Subjects will rest quietly in a fully supine position for at least 10 min before each scheduled timepoint for ECG evaluation. The provider (§ 7.5) will be in charge to provide the devices for continuous monitoring, to train the Phase I Unit personnel in the use of the device, to extract and to analyze the data. Triplicate 10-sec ECGs will be extracted within a time window of 10 min preceding coinciding PK sampling.
ECG tracings will be electronically stored and sent to the central ECG laboratory for analysis at the end of each period.

14.3.3 Tolerance ranges for ECG recording

Actual ECG recording times will be recorded in the individual CRFs. The actual times of recordings should not exceed the recommended tolerance ranges presented in the following table. Any deviation outside the recommended ranges, only in study Part A, will be verified through Data Clarification Forms and, if confirmed, will be reported as protocol deviation.

Actual times of the ECG recordings in Part B will be recorded, but no deviation from the scheduled times will be reported.

Table 14.3.1 Tolerance ranges for the discrete ECG recording in Part A

Scheduled time	Tolerance range
Pre-dose (0) of Day 1	1 h before the start of the injection/infusion
At the end of injection/infusion	+10 min
1, 2 h	+10 min
4 h	+1 h
24 h	+2 h

Date/time of the ECG recording, overall Investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be reported in the individual CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs. Hard copies of the ECGs will be attached to the CRF (See also § 16.3.1).

14.4 Clinical laboratory assays

14.4.1 Hematology, blood chemistry, urine analysis

Samples of blood (12 mL) and urine will be collected. The following laboratory analyses will be performed at the screening visit:

Hematology
Leukocytes and leukocyte differential count, erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, thrombocytes.
Blood chemistry
Electrolytes: sodium, potassium, calcium, chloride, inorganic phosphorus
Enzymes: alkaline phosphatase, γ-GT, AST, ALT
Substrates/metabolites: total bilirubin, creatinine, glucose, urea, uric acid, total cholesterol, triglycerides
Proteins: total proteins
Serum pregnancy test (women): serum b-HCG test.
Urine analysis
Urine chemical analysis (stick)**:** pH, specific weight, appearance, color, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, hematic pigments, leukocytes
Urine sediment (analysis performed only if positive): leukocytes, erythrocytes, flat cells, round cells, crystals, cylinders, mucus, bacteria, glomerular erythrocytes

The same analyses, except for the pregnancy test, will be performed at the final visit / ETV of Part A and, in Part B, at the end of period 1 (Day 13) and on Days -1 and 11 (corresponding to the Final visit/ETV) of period 2.

14.4.2 Serum virology

Hepatitis B (HBs antigen), **Hepatitis C** (HCV antibodies), **HIV 1/2** (HIV Ag/Ab combo) will be assayed at the screening visit in both study Parts.

14.4.3 Urine drug test

A urine drug test will be performed at the Phase I Unit at screening of both study Parts, using a urine multi-drug test kit. The test will be repeated upon confinement on Day -1 of Part A and in both periods of part B.

14.4.4 Pregnancy tests

A serum pregnancy test will be performed at the clinical laboratory (7.4) at screening of both Parts.
Urine pregnancy tests will be performed at the Phase I Unit on Day -1 and Final visit / ETV in Part A and on Day -1 and 13 of period 1 and Day -1 and 11 of period 2 in Part B (Test on Day 11 of period 2 corresponding to the Final visit / ETV test).

14.4.5 Data management

Date/time of samples collections, overall Investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be reported in the individual CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs. Hard copies of the laboratory print-outs will be attached to the CRFs.

14.5 Sampling for pharmacokinetic analysis

14.5.1 Venous blood sampling

Venous blood samples will be collected from a forearm vein through an indwelling catheter or venipuncture at the times summarized in the following table. All blood samples will be withdrawn from the contralateral arm with respect to the arm used for the injection/infusion. The indwelling catheter will be removed at the end of the confinement or before in case of need.

Table 14.5.1.1 Schedule of PK blood sampling

		Blood sampling times after the start of T or R treatment								
	T injection of								**Reference product infusion of**	
	2 min		**5 min**		**15 min**		**30 min**		**30 min**	**30 min**
	Part A	**Part B**	**Part A**	**Part B**	**Part A**	**Part B**	**Part A**	**Part B**	**Part A (Ra)**	**Part B (R)**
Pre-dose	X	X	X	X	X	X	X	X	X	X
2 min	X	X								
5 min	X	X	X	X						
10 min	X	X	X	X						
15 min	X	X	X	X	X	X				
20 min	X	X	X	X	X	X				
30 min	X	X	X	X	X	X	X	X	X	X
45 min	X	X	X	X	X	X	X	X	X	X
1 h	X	X	X	X	X	X	X	X	X	X
1.5 h	X	X	X	X	X	X	X	X	X	X
2 h	X	X	X	X	X	X	X	X	X	X

		Blood sampling times after the start of T or R treatment								
	T injection of								Reference product infusion of	
	2 min		5 min		15 min		30 min		30 min	30 min
	Part A	Part B	Part A	Part B	Part A	Part B	Part A	Part B	Part A (Ra)	Part B (R)
3 h	X	X	X	X	X	X	X	X	X	X
4 h	X	X	X	X	X	X	X	X	X	X
8 h	X	X	X	X	X	X	X	X	X	X
12 h	X	X	X	X	X	X	X	X	X	X
24 h	X	X	X	X	X	X	X	X	X	X
48 h		X		X		X		X		X
72 h		X		X		X		X		X
96 h		X		X		X		X		X
120 h		X		X		X		X		X
144 h		X		X		X		X		X
168 h		X		X		X		X		X
192 h		X		X		X		X		X
216 h		X		X		X		X		X
240 h		X		X		X		X		X

T = Fosnetupitant 235 mg in 20 mL IV injectable solution administered at predefined time durations (30, 15, 5 and 2 min);
R = Fosnetupitant/palonosetron 235 mg/0.25 mg (IV Akynzeo FDC) 20 mL liquid formulation diluted to 50 mL and administered in 30 min (Part B);
Rα = Fosnetupitant/palonosetron 235 mg/0.25 mg (IV Akynzeo FDC) 20 mL liquid formulation, undiluted and administered in 30 min (Part A).

All the scheduled samples will be collected at the given times counted from the start of the injection/infusion. However, if, for whatever reason, a premature interruption of injection/infusion is needed or if a duration longer than that initially scheduled is needed, the sampling scheduled at the end of injection/infusion is to be moved to the actual end time.
Actual sampling times for each subject will be recorded in the individual CRFs. The actual sampling times should not exceed the recommended tolerance ranges presented in the following table. Any deviation outside the recommended ranges will be verified through Data Clarification Forms and, if confirmed, will be reported as protocol deviation, although it will not automatically lead to the exclusion of the concerned subjects from the PK Sets.

Table 14.5.1.2 Tolerance ranges for the scheduled blood sampling times for PK analysis

Sampling time	Tolerance range
Pre-dose (0)	Within 30 min before T or R treatment administration
2 min, 5 min, 10 min, 15 min, 20 min, 30 min	0 min
45 min, 1 h, 1.5 h, 2 h	± 2 min
3 h, 4 h, 8 h, 12 h, 24 h	± 5 min
48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 192 h, 216 h, 240 h	± 60 min

Actual sampling times for each volunteer will be recorded in the individual CRFs.

Blood samples (6 mL each) for PK analysis will be collected using an indwelling catheter with switch valve during confinement. The indwelling catheter for blood collection will be placed on the contralateral arm with respect to the infusion arm. The cannula will be rinsed, after each sampling, with about 1 mL of sterile saline solution containing 20 I.U./mL Na-heparin. The first 1.5 mL of blood will be discarded at each collection time to wash the cannula out of saline

solution and avoid diluting the analyte concentrations. The remaining volume of 4.5 mL of blood will then be collected from the catheter and transferred with a syringe into K_2EDTA tubes. Blood samples will be immediately centrifuged at 1500 g for 15 min at 4° C to obtain plasma. If immediate centrifugation is not possible, blood samples will be kept on melting ice or in a refrigerator at 4° C for a maximum of 1 h. Each plasma sample will be divided at room temperature within a maximum of 4 h from blood centrifugation into 6 pre-labeled tubes: F1 and F2 (both of at least 200 µL) for the assay of fosnetupitant, N1 and N2 (both of at least 500 µL) for the assay of netupitant and its metabolites. For the collection of the 3rd aliquots (F3 and N3), the remaining plasma will be used. Plasma samples will be stored frozen at ≤-70° C (F and N aliquots) until analysis.

If any clinical assessment, such as vital sign measurement or ECG recording, is foreseen at the same time-point as blood sampling for PK analysis, blood collection will be performed at the scheduled time. Vital signs and ECG recordings for immediate safety evaluation can be performed before the pre-dose sampling and after the post-dose samplings, but inside the recommended tolerance ranges presented in Table 14.2.1 and Table 14.3.1. Any deviations outside the recommended time ranges will be verified through Data Clarification Forms and reported as a protocol deviation. Discrete ECGs will be extracted from the continuous monitoring by the provider before blood sampling scheduled at the same time point.

14.5.2 Analytics

The plasma concentrations of fosnetupitant, netupitant and its main metabolites will be determined at Ardena Bioanalysis BV, the Netherlands, using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical methods with appropriate lower limits of quantification (LQL).

Analyses will be performed according to the general Principles of “OECD Good Laboratory Practices for testing of chemicals" C(81) 30 (final) and GCP.

The analytical reports will be attached to the final report.

14.5.3 Labelling, storage and transport of samples

14.5.3.1 Samples labelling Please modify as applicable

Each sample tube will be clearly and unequivocally identified with a label resistant to the storage temperature and reporting:

Study code	Study CRO-PK-22-363 - Sponsor code PNET-22-08
Subject number	001-066 (for Part A); 101-140 (for Part B)
Tube identification	F1, F2, F3, N1, N2, N3,
Study Part	Part A/ Part B
Period	1 or 2 (Part B only)
Scheduled sampling time	as min or h; see § 14.5.1

14.5.3.2 Samples storage and transport

At the Phase I Unit, aliquots N1, N2, N3, F1, F2 and F3 will be stored at ≤-70° C. At the end of each collection day, the aliquots will be stored in 2 separate freezers.

All aliquots 1, packed in sufficient solid CO_2, will be shipped by an authorized courier from CROSS Research S.A. Phase I Unit, Switzerland, to Ardena Bioanalysis BV, the Netherlands. Aliquots 1 will remain stored at the laboratory for a maximum time of 3 months after a QA audited bioanalytical report is issued. Afterwards, the samples will either be destroyed or returned or stored for a longer period in agreement with the Sponsor. In case the sample destruction is chosen, a certificate of destruction will be provided to the Sponsor.

The back-up samples (aliquots 2 and 3) will remain stored at CROSS Research S.A., Switzerland. These samples could either be:

- sent to the laboratory for reanalysis, should this become necessary for analytical reasons or if any problems occur during the delivery or analysis of aliquots 1, or
- destroyed at an authorized site, or
- transferred to the Sponsor upon written request, or
- stored at CROSS Research S.A., for a maximum time of 5 years

No analyses different from those stated in this protocol and agreed by the subjects when signing the informed consent form will be performed unless a new informed consent and a new approval from the Ethical Committee is obtained. The subjects may ask to destroy their own samples at any time.

14.6 Total number of samples and blood withdrawn

During the study the following volume of blood will be collected from each subject, in the relevant study part:

For routine (safety) laboratories analysis of Part A:

Screening visit:	12 mL
Final visit/ETV:	12 mL

For routine (safety) laboratories analysis of Part B:

Screening visit:	12 mL
End of period 1:	12 mL
Confinement for period 2:	12 mL
Final visit/ETV:	12 mL

For PK analysis:

Part A:	from a minimum of 11x6 mL=66 mL to a maximum of 16x6 mL=96 mL, depending on durations of injection tested in the cohorts
Part B:	from a minimum of 20x2x6 mL=240 mL to a maximum of (20x6 mL) + (25x6 mL)=270 mL, depending on the injection duration

The maximum total volume of blood which could be withdrawn from each subject in part A will be 120 mL (safety + PK analyses), over a maximum study duration of 28 days.

The maximum total volume of blood which could be withdrawn from each subject in part B will be of 318 mL (safety + PK analyses) over a study duration of 55 days or longer. In either case the total volume of blood withdrawn will not exceed a standard blood donation.

15 ASSIGNMENT OF STUDY TREATMENT

15.1 Randomization

Cohorts of Part A are not randomized.

The randomization lists for Part B will be computer-generated by the Biometry Unit of the CRO, using the PLAN procedure of SAS® version 9.3 (TS1M1) (13) or higher (the actual version will be stated in the CSR). The randomization list will be attached to the final CSR.

15.2 Treatment allocation

In cohort 1 of Part A, the subjects will be assigned to one parallel treatment (T or Rα) according to their admittance to the Phase I Unit, i.e., the first 10 subjects will receive Rα and the next ten T. In study part B, the subjects will be assigned to one of 2 sequences of treatments (e.g., T-R or R-T) according to their randomization number that will be given to the subjects on study Day -1, period 1.

The treatments will be assigned to the subjects through opaque sealed envelopes. Each envelope will report the randomization number on the label and the treatment inside and it will be opened at the time of randomization for each patient. The randomization letters will be generated through a dedicated SAS program based on the randomization list. The Investigator or his deputy in charge of the randomization number assignment will have no access to the complete randomization list, thus being unaware of the sequences corresponding to each randomization number.

15.3 Blinding

This is an open-label study. No masking procedure will be applied.

16 EVALUATION PARAMETERS

16.1 Study endpoints

16.1.1 Primary endpoints

16.1.1.1 Primary endpoint of Part A

- Type, number and frequency of TEAEs collected up to 24 h post-dose.

16.1.1.2 Primary endpoint of Part B

- Area under the plasma concentration-time curve of netupitant from time zero to the time of last measurable concentration or to infinity (AUC_{0-t} and $AUC_{0-\infty}$) following administration of T, at the infusion duration selected in Part A, and R administered as a 30-min diluted infusion.

16.1.2 Secondary endpoints

16.1.2.1 Secondary safety endpoints of Part A

- Vital signs (blood pressure, pulse rate), 12-lead ECG, clinical laboratory tests (blood chemistry, hematology and urinalysis), body weight and physical examination

16.1.2.2 Secondary safety endpoints of Part B

- Safety and tolerability parameters of T versus R (TEAEs, vital signs [blood pressure, pulse rate], 12-lead ECG, clinical laboratory tests (blood chemistry, hematology and urinalysis), body weight and physical examination.
- Cardiac evaluation:
  - Placebo-corrected change from baseline in HR, QT, QTcF, QTcB, PR and QRS intervals.
  - Change from baseline in HR, QT, QTcF, QTcB, PR and QRS intervals.
  - Categorical outliers for HR, QT, QTcF, QTcB, PR, and QRS intervals.
  - Frequency of changes in T-wave morphology and U-wave presence from triplicate 12-lead ECGs extracted from continuous recordings.

16.1.2.3 Secondary PK endpoints of Part A and B

For plasma fosnetupitant, netupitant and its main metabolites M1, M2 and M3, when applicable, the following parameters will be measured/calculated:

- C_0, C_{max}, t_{max}, C_{last}, t_{last}, AUC_{0-t} (for all analytes with exception of netupitant AUC_{0-t} in Part B, which is the primary endpoint), AUC_{0-24}, λ_z, $t_{½}$, CL, V_z, MRT

16.1.2.4 Secondary PK endpoints of Part B only

For plasma fosnetupitant, netupitant and its main metabolites M1, M2 and M3, when applicable, the following parameters will be measured/calculated:

- AUC_{0-120}, $AUC_{0-\infty}$ (with exception of netupitant $AUC_{0-\infty}$, which is the primary endpoint)

For plasma fosnetupitant, the following parameter will be calculated:
- $RAUC_{fos/netu}$

For plasma M1, the following parameter will be calculated:
- $RAUC_{M1/netu}$

For plasma M2, the following parameter will be calculated:
- $RAUC_{M2/netu}$

For plasma M3, the following parameter will be calculated:
- $RAUC_{M3/netu}$

16.2 Pharmacokinetic assessments

16.2.1 Pharmacokinetic parameters

The following PK parameters will be measured and/or calculated, when applicable, for plasma fosnetupitant, netupitant and its metabolites in both parts, using the validated software Phoenix WinNonlin® version 8.3.5 (13) or higher (actual version will be stated in the final report):

$C_{0:}$	Plasma concentration at the end of the injection or infusion
C_{max}:	Maximum plasma concentration
t_{max}:	Time to achieve C_{max}
C_{last}:	Last measurable plasma concentration above the LQL of the bioanalytical method
t_{last}:	Time of C_{last}
AUC_{0-t}:	Area under the concentration-time curve from time zero to t_{last}, calculated by the linear trapezoidal method
AUC_{0-24}:	Area under the plasma concentration-time curve from time zero to 24 h
λ_z:	Terminal elimination rate constant, calculated, if feasible, by log-linear regression using at least 3 points, C_0 and C_{max} excluded
$t_{1/2}$:	Apparent terminal half-life, calculated, if feasible, as $\ln 2/\lambda_z$
CL:	Systemic clearance
V_z:	Apparent volume of distribution in the post-distribution phase

MRT: Mean residence time

The following PK parameters will be calculated for netupitant and its metabolites only in Part B:

$AUC_{0\text{-}120}$ Area under the plasma concentration-time curve from time zero to 120 h

$AUC_{0\text{-}\infty}$: Area under the concentration-time curve from time zero to infinity, calculated, if feasible, as $AUC_{0\text{-}t} + C_{last}/\lambda_z$

$\%AUC_{extra}$: Percentage of $AUC_{0\text{-}inf}$ extrapolated from t_{last} to infinity as $100\times[(C_{last}/l_z)/AUC_{0\text{-}inf}]$

The following PK parameter will be calculated for fosnetupitant only in Part B:

$RAUC_{fos/netu}$: Molecular weight-normalized fosnetupitant to netupitant $AUC_{0\text{-}\infty}$ ratio

The following PK parameter will be calculated for M1 only in Part B:

$RAUC_{M1/netu}$: Molecular weight-normalized M1 to netupitant $AUC_{0\text{-}\infty}$ ratio

The following PK parameter will be calculated for M2 only in Part B:

$RAUC_{M2/netu}$: Molecular weight-normalized M2 to netupitant $AUC_{0\text{-}\infty}$ ratio

The following PK parameter will be calculated for M3 only in Part B:

$RAUC_{M3/netu}$: Molecular weight-normalized M3 to netupitant $AUC_{0\text{-}\infty}$ ratio

The sampling schedule is considered adequate if the ratio $AUC_{0\text{-}t}/AUC_{0\text{-}\infty}$ equals or exceeds a factor of 0.8 (i.e., if $\%AUC_{extra}$ is <20%) for more than 80% of the individual PK profiles. This assures that the primary variable $AUC_{0\text{-}t}$ covers a sufficient percentage of the theoretical total extent of exposure. $AUC_{0\text{-}\infty}$ values with $\%AUC_{extra}$ greater than 20% will be flagged but included in the summary statistics.

The quality of log-linear regression (and, consequently, the reliability of the extrapolated PK parameters) should be demonstrated by a determination coefficient $R^2 \geq 0.8$. Individual extrapolated parameters, when considered unreliable, will be reported as NC (not calculated).

16.3 Safety assessments

Safety and general tolerability of T versus R will be based on TEAEs, physical examinations including body weight, vital signs, 12-lead ECG and routine hematology, blood chemistry and urinalysis laboratory tests.

16.3.1 Cardiodynamic ECG assessment for Part B

The following ECG parameters will be measured and calculated: HR, PR, QT, Fridericia corrected QTc (QTcF), Bazett corrected QTc (QTcB), QRS.

T-wave morphology and U-wave presence will be assessed.
Statistical methodology for the cardiac evaluation endpoints is presented in § 17.5.7.

17 STATISTICAL METHODS

The data documented in this study and the parameters measured will be evaluated and compared using classic descriptive statistics, i.e., geometric mean (PK data only), arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables.

Not available data will be evaluated as "missing values". The statistical analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1) (13) or higher (the actual versions will be stated in the final report).
The statistical analysis of PK parameters will be performed using Phoenix WinNonlin™ version 8.3.5 (14) or higher and SAS® version 9.3 (TS1M1) or higher.
Further details of the statistical analyses and data presentations to be used in reporting the study will be provided in the Statistical Analysis Plan (SAP).

Demographic, safety, and PK analyses will be performed by the Biometry Unit of the CRO (§ 7.6), while ECG statistical analysis will be performed by the provider of continuous ECG (§ 7.5).

17.1 Analysis Sets

17.1.1 Definitions

A subject will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures.

A subject will be defined as eligible if he/she meets all the inclusion/exclusion criteria. Otherwise, he/she will be defined as a screen failure.

A subject will be defined as enrolled in the study if he/she is included in the interventional phase of the study. The enrolment will be performed through a non-randomized or randomized inclusion in the study.

An eligible but not enrolled subject will be defined as a reserve.

- Enrolled set: all enrolled subjects. This analysis set will be used for demographic, baseline and background characteristics
- Safety set: all subjects who receive at least one dose of the IMPs, including partial administration. This analysis set will be used for the safety analyses
- PK set A: all enrolled subjects who fulfill the study protocol requirements in terms of T or Rα administration and have evaluable PK data readouts, with no major deviations that may affect the PK results. This analysis set will be used for the statistical analysis of the PK results of study Part A
- PK set B: all enrolled subjects who fulfill the study protocol requirements in terms of T and R administration and have evaluable PK data readouts for the planned treatment

comparisons, with no major deviations that may affect the PK results. This analysis set will be used for the statistical analysis of the PK results of study Part B

Each subject will be coded by the CRO Biometry Unit as valid or not valid for the Safety set, PK set A and PK set B. Subjects will be evaluated according to the treatment they actually receive.

17.1.1.1 Reasons for exclusion from the PK set before bioanalysis

Reasons for the exclusion of subjects from one period in the PK set are the following:

- intake of concomitant medications or food / beverages which could render the plasma concentration-time profile unreliable
- AEs which could render the plasma concentration-time profile unreliable
- administration errors which could render the plasma concentration-time profile unreliable
- other events which could render the plasma concentration-time profile unreliable

If one of these events occurs, it will be noted in the CRF as the study is being conducted.

17.1.1.2 Reasons for exclusion from the PK set B after bioanalysis

Exclusion of subjects on the basis of PK reasons is possible only for:

- subjects with lack of any measurable concentrations or only very low plasma concentrations of netupitant. A subject is considered to have very low plasma concentrations if his/her AUC is less than 5% of netupitant geometric mean AUC (which should be calculated without inclusion of data from the outlying subject)
- subjects with implausible concentrations (i.e., different from the known, expected concentration profiles) of netupitant. The exclusion of these subjects must be justified on the basis of sound scientific reasons and mutually agreed between the CRO and the Sponsor
- subjects with non-zero baseline concentrations > 5% of C_{max}

The samples from the subjects excluded from PK set B after bioanalysis should still be assayed and the results listed. Subjects should not be excluded from PK set B if the AUC_{0-t} covers less than 80% of the $AUC_{0-\infty}$.

17.2 Sample size and power considerations

The planned number of 20 healthy subjects to be included in cohort 1 and of 10 healthy subjects to be included in each following cohort of Part A (cohorts 2, 3 and 4) of the study was not computed by statistical assumptions.

The sample size for the netupitant exposure equivalence (netupitant AUC) assessment in Part B of the study, will be 40 healthy male and female subjects in order to have 34 completed subjects. Drop-outs will not be replaced. The sample size was determined by a statistical power calculation to test equivalence based on AUC_{0-t}. The assumptions are that the expected ratio of means is 1 (Fosnetupitant 235 mg IV versus Akynzeo IV injection), the cross-over ANOVA √MSE (ln scale) is 0.265, and α is 10% (bilateral). A sample size in each sequence group of 17 (total sample size is 34) is required to have a power of 90%.

17.3 Demographic, baseline and background characteristics

Critical demographic characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarized in contingency tables. Quantitative data will be summarized using classic descriptive statistics.

17.4 Analysis of pharmacokinetic parameters

17.4.1 Descriptive pharmacokinetics

A descriptive PK will be presented. The results will be displayed and summarized in tables and figures. Individual curves at actual sampling times and mean curves (+SD) at scheduled sampling times will be plotted. Data below the lower quantification limit (BQL) will be considered as 0 in the calculations of mean concentrations and "missing data" in individual concentration-time plots. For the estimation of PK parameters, BQL concentrations will be considered as 0 at early time points (i.e., time points before C_{max}) and "missing data" at later time points, including the terminal part of the curve. They will be presented as BQL in listings and tables. As a consequence of BQL values, calculated geometric means (if requested) could be null. For this reason, in the presence of any null value, the geometric mean will be reported as not calculated (NC).

17.4.2 Statistical comparison of pharmacokinetic parameters

According to the current FDA Guideline on the bioavailability and bioequivalence studies (9), AUC_{0-t} and $AUC_{0-\infty}$ of plasma netupitant of study Part B will be analyzed using analysis of variance (ANOVA). Before analysis, the data will be transformed using a neperian logarithmic transformation. The statistical analysis will take into account treatment, period, sequence and subject within sequence as fixed effects. The parametric point estimators (PE) for the ratios of treatments and 90% CI will be calculated using the adjusted least squares means from the ANOVA. Results for the log-transformed exposure measures will be then back-transformed to obtain point estimators (i.e., geometric mean ratio) and two-sided 90% CI as percentages.

The statistical method for testing bioequivalence is based upon the 90% CI for the T/R ratio of the least square geometric means of the parameters under consideration. Acceptance criterion

for bioequivalence will be a 90% CI of the ratio of geometric means (PE) within the 80.00 – 125.00% range.
While the equivalence of the selected T and R will be assessed based on the netupitant AUC_{0-t} and $AUC_{0-\infty}$ estimates, the T/R geometric mean ratio and the relevant 90% CI will also be calculated for other exposure measures, including netupitant AUC_{0-120} and C_{max}. The T/R geometric mean ratio and the relevant 90% CI will also be calculated for exposure measures of M1, M2 and M3, including AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-120} and C_{max}.
The peak time, t_{max}, of T and R will be analyzed using a non-parametric test applied to untransformed data.

17.5 Safety and tolerability evaluation

17.5.1 Adverse events

AEs will be coded by System Organ Class (SOC) and PT, using the Medical Dictionary for Regulatory Activities (MedDRA).
AEs will be classified as pre-treatment AEs (PTAEs) and TEAEs, according to the period of occurrence, as follows:

- PTAEs: all AEs occurring from the signature of the informed consent to participate in the study up to the first T or R dose, including AEs occurring after P and before T or R in Part B
- TEAEs: all AEs occurring after the first dose of T or R

Individual PTAEs and TEAEs will be listed in subject data listings. No summary table will be provided for PTAEs. TEAEs will be summarized by treatment and overall. The number and percentage of subjects with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity.

17.5.2 Physical examination

Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed.

17.5.3 Laboratory data

Date/time of samples collection, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be listed. All laboratory results will be listed and a table of all the abnormal values will be presented. The overall investigator's interpretation will be summarized using tables of frequency.

17.5.4 Vital signs

Vital signs values will be listed and summarized by descriptive statistics.

17.5.5 Body weight

Body weight values at screening and final visit/ETV will be listed and summarized by descriptive statistics.

17.5.6 ECG for immediate safety

Date/time of ECG recordings, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed. The overall investigator's interpretation will be summarized using tables of frequency.

17.5.7 Continuous ECG

For the cardiac safety evaluation and further analyses, 10-sec triplicate ECGs will be extracted within a time window of 10 min preceding PK sampling and evaluated (§ 14.3).
The QT interval will be presented raw and after HR correction using the Fridericia formula as primary endpoint. ECG data will be listed and summarized highlighting differences from baseline for quantitative variables and frequencies of treatment emergent abnormalities. The number of QTc values above 450 ms, 480 ms and 500 ms at each evaluation timepoint will be tabulated, jointly with its change from baseline. Likewise, values differing by more than 30 ms from the baseline at each time point will be tabulated.

Data from Holter continuous recording will be assessed in blind by the provider (§ 7.5) according to a centralized procedure.

The primary analysis will be based on exposure response modeling of the relationship between netupitant and its metabolites M1, M2 and M3 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect >10 ms at clinically relevant plasma concentrations of netupitant, M1, M2 and M3.

In addition, the effect of netupitant on the placebo-corrected ΔQTcF, ΔHR, ΔPR, ΔQRS, ΔQT, and ΔQTcB (ΔΔQTcF, ΔΔHR, ΔΔPR, ΔΔQRS, ΔΔQT, and ΔΔQTcB) will be evaluated at each post-dose timepoint ('by timepoint' analysis) using the Intersection Union Test. An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QT, QTcF, QTcB, T-wave morphology and U-wave presence.

See also § 16.3.1.

18 DEFINITION AND HANDLING OF AEs AND SAEs

18.1 Applicable SOPs

AEs definition, classification and management will follow the Sponsor's SOPs, based upon applicable local and international regulations. The full SOP or an operative summary will be made available to the clinical center.

A brief summary of AE definition, classification and management is reported below.

18.2 Definition of Adverse Events

AE
As defined by the current ICH Guideline for Good Clinical Practice (15) an AE is:
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.
Within the scope of this study, such untoward medical occurrences would be considered as "AEs" even if the subject was not administered the study drugs but had already signed the informed consent form.
AEs include the following types of occurrences:

- Suspected adverse drug reactions
- Other medical experiences, regardless of their relationship to the study drugs, such as injury, surgery, accidents, increased severity of pre-existing symptoms, apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, physiological testing, or physical examination findings
- Reactions from drug overdose, abuse, withdrawal, hypersensitivity, or toxicity.

SAE
A SAE is any event that suggests a significant hazard, contraindication, side effect, or precaution, whether it is considered or not to be associated with the study product. A SAE is an AE that meets any of the following criteria:

- Results in death. This includes any death that occurs during the conduct of a clinical study, including deaths that appear to be completely unrelated to the study drugs (e.g., car accident).
- Is life-threatening. This includes any AE during which the subject is, in the view of the Investigator, at immediate risk of death from the event as it occurs. This definition does not include events that may have caused death if they had occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Other medical events that based upon appropriate medical judgment are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

Unexpected Adverse Event
An Unexpected Adverse Event is any experience not previously reported (in nature, severity or incidence) in the current Investigator's Brochure for fosnetupitant/netupitant/palonosetron (Reference Safety Information) (4).
Pre-existing Condition
A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

18.3 Classification of Adverse Events

The Investigator will classify AEs based on their severity and relationship to treatment. Every effort must be made by the Investigator to categorize each AE according to its severity (see below), and its relationship separately either to netupitant, palonosetron or both (see § 18.3.1).

18.3.1 Severity

For this trial, the intensity of an AE will be rated according to the following definitions:

Mild
Symptom barely noticeable to subject; does not influence performance or functioning. Prescription medication is not ordinarily needed for relief of symptom but may be given because of the personality of a subject.

Moderate
Symptom of a sufficient intensity to make a subject uncomfortable; performance of daily activities influenced; subject is able to continue the trial; treatment for symptom may be needed.

Severe
Symptom causes severe discomfort. May be of such intensity that a subject cannot continue the trial. Intensity may cause cessation of treatment; treatment for symptom may be given and/or subject hospitalized.

18.3.2 Relationship to Investigational Medicinal Product

For this trial, an AE cause and effect relationship to the study drug will be classified by the Investigator as reported hereafter.

Definitely related
The event:
- Follows, in a reasonable temporal sequence, the administration of the drug or the drug level that has been established in body fluids or tissues.
- Follows a known or expected response pattern of the suspected drug.

- Is confirmed by improvement after de-challenge or dosage reduction of the drug.
- Reappears after repeated exposure (re-challenge).

Probably related
The event:
- Follows, in a reasonable temporal sequence, the administration of the drug.
- Follows a known or expected response pattern of the suspected drug.
- Is confirmed by improvement after de-challenge or dosage reduction of the drug.
- Cannot be reasonably explained by the known characteristics of the subject's clinical state.
- No re-challenge test or laboratory confirmation is available.

Possibly related
The event:
- Follows, in a reasonable temporal sequence, the administration of the drug.
- Follows a known or expected response pattern of the suspected drug but could have been easily produced by a number of other etiologies.

Unlikely related
There is no reasonable temporal association between the drug and the AE or the event could have been related to the subject's clinical state or concomitant treatment(s), or another cause adequately explaining the AE is known or is much more probable.

Not related / None
Sufficient information exists indicating that etiology is unrelated to the drug.

Unassessable
The data are insufficient or contradictory to make a meaningful medical assessment. This criterion should be used only in case of insufficient evidence, conflicting data or poor documentation. Every effort should be done by the Investigator to make appropriate assessment of causal relationship.

18.3.3 Reporting Adverse Events

AE reporting has to be in accordance with the ICH E6 Guidance on GCP and ICH E2A Guidance on Clinical Safety Management (15, 16).
During the course of the study, all AEs (including SAEs), irrespective of the relatedness to the study drugs, must be recorded in detail in the source records and transcribed onto the AEs pages of the CRF. During each monitoring visit, the Investigator and the site monitor will review all AEs and perform Source Data Verification (SDV). The Investigator will be responsible for ensuring that the correct information concerning all AEs is entered on the appropriate CRF pages.
The reporting period for AEs is the period starting from the time of informed consent signature and lasting until the Final Visit/ETV. All ongoing serious (SAEs and SADRs) and non-serious AEs judged as related to the study treatment will be followed until 14 days after the subject completes the study. All unresolved AEs (including SAEs) will be documented on the CRF as "ongoing" without further follow-up.

18.3.4 Reporting Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

All SAEs occurring from the time of signing of the informed consent until the Final Visit/ETV must be reported immediately to the Sponsor.
Information on the actual fax and phone numbers are provided in the Investigator file as well as in § 18.4.

The Investigator or designated study coordinator must complete the Investigational Serious AE Form and send it to the Sponsor within 24 h of observation or notification of a SAE. All of these events must also be recorded on the appropriate CRF pages.
It is the responsibility of the Investigator to inform his local EC about SAEs according to the local EC requirements. It is the responsibility of the Sponsor to submit applicable SUSAR Reports to the Competent Authorities. Reporting of suspected unexpected serious adverse reactions (SUSARs) to the relevant EC, in accordance with Swiss Ordinance on Clinical Trials with the exception of Clinical Trials of Medical Devices 810.305 (ClinO) of 20 September 2013 (Status as of 26 May 2022), will also be the responsibility of the CRO (15, 16).
A safety contact sheet will be provided to the Investigator and will be maintained in the Investigator file at the Phase I Unit. Refer to the instructions and definitions for completing the Investigational SAE Form for submitting all SAEs to the CRO.

18.3.4.1 Follow-up of SAEs

For Pharmacovigilance purposes only, when the Phase I Unit receives any information about a SAE (related and unrelated) which changes or adds to the information on the initial investigational SAE form, the Phase I Unit will fill out a new investigational SAE form and tick the “follow-up” box of the SAE form and fax it within 24 h to the Sponsor, especially if this new information has an effect on the seriousness, relatedness or expectedness of an AE (please refer to § 18.4 for contact details).

18.3.5 Pregnancy Report

In the unlikely eventuality that a patient becomes pregnant during the trial, the Investigator will be requested to complete the Pregnancy Report Form and any relevant document. They must be forwarded to the Sponsor e-mail address or sent by fax (see § 18.4). Even though pregnancy is not considered as SAE itself, pregnancy has to be reported within the timelines as defined for SAE.
Pregnant subjects will be followed by the Investigator and CRO / Sponsor until the fetus / newborn is delivered. At the study end and database closure, reports of Pregnancy Outcome will be sent by the sites directly to Helsinn (Drug Safety). The subject’s primary care physician (or obstetrician) will be requested by consenting pregnant subjects to provide the Investigator with further information on the pregnancy using the Pregnancy Outcome Information Form. If pregnancy occurs while the subject is on study treatment or up to 28 days after last study drug administration, the subject will be discontinued from the study.

18.4 SAEs: contacts

The clinical site can be contacted using the phone and fax numbers stated in this protocol or calling the mobile phone number +41 79 822 35 07 (operative 24-h/day, 365 days/year). This mobile phone can be called by the study participants to communicate to the clinical staff any SAE occurring outside the clinical facility.

Safety contact at CRO:
Dr. Milko Radicioni
Phone:
Fax:
Email:

Sponsor Drug Safety Officer:

Mario Bertazzoli, MD
Helsinn Healthcare SA
Via Pian Scairolo 9
6912 Lugano, Switzerland

Phone:
Fax:
Email:
(copies to: drug-safety@helsinn.com)

19 SUBJECTS' DISCONTINUATION, STUDY TERMINATION

19.1 Withdrawal of subjects

In case of a subject's premature discontinuation from the study, the primary reason for discontinuation will be recorded.

19.1.1 Primary reason for discontinuation

Primary reason for discontinuation from the study could be one of the following:

- **adverse event**: Any (significant) adverse event that in the opinion of the investigator or concerned subject is not compatible with study continuation. For the definition of AE, please refer to § 18.2.
- **death**
- **lost to follow-up**: the loss or lack of continuation of a subject to follow-up
- **non-compliance with study drug**: an indication that a subject has not agreed with or followed the instructions related to the study medication
- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the subject
- **pregnancy**
- **protocol deviation**: an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by sponsor**: an indication that a clinical study was stopped by its sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by subject**: study discontinuation requested by a subject for whatever reason
- **other**: different than the ones previously specified

19.1.2 Discontinuation procedures

For any subject discontinuing the study, the investigator will:

- ask the subject to undergo, as far as possible, a final medical visit (ETV) to examine the subject's health conditions and perform the required blood sampling for the laboratory assays. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e., not clinically significant changes compared to screening)
- arrange for alternative medical care of the withdrawn subject, if necessary
- record the subject decision about the use of collected biological samples
- report in the CRF date and time of the last dose administration, and date and primary reason of study discontinuation

- record in the CRF any follow-up, if the subject is withdrawn for an AE

In either study part, discontinued subjects will not be replaced after assignment of the study number (Part A) or randomization number (part B).

Subjects who will not be assigned a study number (Part A) or randomization number (part B) in the evening of Day -1 and discontinuing at that time, will be replaced by reserve subjects.

19.2 Study termination

The study will be considered terminated at the date of the last visit of the last subject entered in study part B or upon completion of any follow-up procedure described in protocol. The Investigator and the Sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation must be documented appropriately.

With respect to the stopping rules defined for study Part A only, please refer to § 13.2.

20 DATA MANAGEMENT PROCEDURES

20.1 Data collection – CRFs

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the CRFs. He must also check that the data reported in the CRFs correspond to those in the subject's source documents for all subjects who have been included in the study.
To ensure legibility, the CRFs should be filled out in English, in block capitals with a ball-point pen (not pencil, felt tip or fountain pen). Any correction to the CRFs' entries must be carried out by the investigator or a designated member of staff. Incorrect entries must not be covered with correcting fluid, or obliterated, or made illegible in any way. A single stroke must be drawn through the original entry. Corrections must be dated and initialed. In the interest of completeness of data acquisition, the questions which are repeated in each section of the CRFs should be answered in full, even if there are no changes from a previous examination. The investigator must provide a reasonable explanation for all missing data.
The CRFs will be completed, signed by the investigator, sent to the CRO Biometry Unit for data management procedures and finally sent to the sponsor.
Subject's source documentation (i.e., volunteer's medical records and study source documents) will be maintained at the Phase I Unit. Source data verification will be regularly performed by the study monitors (See also § 21.1). The sponsor and the CRO are responsible for the data management of this study including quality checking of the data, each one for their respective activities.

20.2 Unique subject identifier

All the subjects who sign the informed consent form for each part of the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique subject identifier consists of the sponsor study code (i.e., PNET-22-08), the 3-digit site number (i.e., 001), the 4-digit screening number for Part A (e.g., S001, S002, etc.) or the 4-digit screening number for Part B (e.g., S101, S102, etc.) and, if applicable, the 3-digit subject study number for Part A (e.g., 001, 002, etc.) or the 3-digit subject randomization number for Part B (e.g., 101, 102, etc.). Study code, site number, screening number and subject study or randomization number are separated by slashes ("/"). The last 8 digits of the unique subject identifier (enrolled subjects), corresponding to the subject screening and subject study or randomization numbers separated by a slash, or the last 4 digits of the unique subject identifier (not enrolled subjects), corresponding to the subject screening number, will appear as subject identifier in the individual listings and figures of the clinical study report and will be used to identify the subjects in in-text tables or wording (if applicable).

20.3 Database management

The CRO will provide a double data entry with total re-entry of data by a second data entrist and discrepancy resolution by a third individual and will update and verify the database and create the final SAS data sets. The final data file will be transferred to the sponsor in the agreed format with all the other study documentation.

20.3.1 Coding dictionaries

Medical/surgical history and underlying diseases, clinically significant physical examination abnormalities and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™).
Previous and concomitant medications will be coded using the WHO Drug Dictionary Enhanced (WHODDE). The version of the coding dictionaries will be stated in the study report.

21 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

21.1 Monitoring

The monitoring visits will be conducted by appropriate staff selected by the CRO.

Monitoring activities, including monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures, monitoring reports will comply with ICH-GCP chapter 5.18 requirements.

Adequate time and availability for monitoring activities should be ensured by the investigator and key study personnel.

Data verification is required and will be done by direct comparison with source documents, always giving due consideration to data protection and medical confidentiality. In this respect the investigator will assure support to the monitor at all times.

The Investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing authorized individuals to have access to all the study documentation. In addition to the monitoring activities performed by the study monitor, the sponsor and/or sponsor's delegates could perform on-site study audits in order to ensure the study compliance with the study procedures, the ICH-GCP guidelines and the applicable regulatory requirements. The auditing activities may also be conducted after study completion.

21.2 Quality Control and Quality Assurance

The CRO has implemented and maintains a Quality System with written SOPs to ensure that the study is conducted in compliance with the protocol and all effective amendments, ICH-GCP, and the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOAC++ principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete-Consistent-Enduring-Available-Traceable).

The clinical site(s) is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

The CROs and the sponsor will be responsible for their respective activities.

The sponsor may transfer any or all the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

21.3 Applicable SOPs

The Sponsor, the Phase I Unit and the CRO will follow their respective SOPs in the conduct of the respective activities, unless otherwise stated in written agreements. SOPs will be made available for review, if required.

21.4 Data access

The investigator and the CRO will ensure that all raw data records, medical records, CRFs and all other documentation that is relevant to this study will be made accessible for monitoring activities, audits, IEC review, and regulatory inspections.

21.5 Audits and inspections

The sponsor, independent bodies acting on behalf of the sponsor and the CRO have the right to perform audits according to ICH-GCP responsibilities.

The study may also be inspected by regulatory authorities. If a regulatory authority notifies the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the investigator must inform the study sponsor and the CRO immediately.

The investigator and the CRO agree, by written consent to this protocol, to fully co-operate and support audits and inspections compliance checks by allowing authorized individuals to have access to all the study documentation.

22 ETHICAL CONSIDERATIONS

22.1 Ethics and Good Clinical Practice (GCP)

The study will be performed in accordance with the relevant guidelines of the Declaration of Helsinki.
The approval of the study protocol by the local (Canton Ticino) IEC and by the Federal Health Authorities (Swissmedic) will be obtained before the start of the study.

The present clinical study will be carried out according to the current revision of Good Clinical Practice (GCP), ICH topic E6 (R2), and the applicable local law requirements.

22.2 Informed consent

Before being enrolled into the clinical study, the subjects must have provided their written consent to participate, after the Investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study or relevant study Part. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language by the CRO and must be approved by the EC and may further be updated as new important information becomes available that may affect subject's willingness to participate or continue in the trial.
It will include all the elements required by law according to the ICH-GCP recommendations and regulatory requirements.

The informed consent form will inform potentially eligible subjects about the nature of the study drugs, their efficacy and safety profile, the route of administration, and the human experience available. It will also outline the steps of the protocol, as they will apply to the individual, including the number of visits and types of procedures/assessments/measurements to be performed so that the individual has a clear picture of the risks, inconveniences and benefits that may accrue from the trial. The subject must be made aware that he/she may refuse to join the trial or may withdraw his/her consent at any time without prejudicing further medical care and that he/she is covered by the sponsor indemnity insurance in the event of a trial related injury. Contact details to report and discuss suspected trial-related injuries will be provided. The subjects must also know that their personal medical records may be reviewed in confidence by the staff of sponsor or representatives to the extent permitted by the Data Protection Laws or other applicable regulations and by regulatory authorities and IRB/EC and that personal information will be collected and retained in a confidential database under the control of the Investigator/study site. Conditions for ensuring the codification/de-identification of data and the methods used to ensure the security and confidentiality of the database should be explained. Consent will always be expressed in writing after the subject has had adequate time to review the information and to ask questions, if need be.
Adequate time and opportunity to satisfy questions will be given to the subjects and the time will be recorded. The signed information sheet and informed consent form must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol).

Subjects will be provided with information prepared in the local language, the processing of personal data will be in strict compliance with the “Data Protection Laws", as defined below (see § 23.5).

The Investigator will be supplied with an adequate number of blank informed consent forms to be used. The forms will be signed and dated by both the Investigator and the subject.
A copy of the signed form will be given to the subject.

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the Investigator's study file according to the regulatory requirements (see § 23.3). The Investigator will allow inspection of the forms by authorized representatives of the sponsor, EC members and regulatory authorities. He will confirm, by signing and dating the forms, that informed consent has been obtained.

22.3 Insurance policy

An insurance cover has been issued in favor of the subjects participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

23 ADMINISTRATIVE PROCEDURES

23.1 Material supplied to the Phase I Unit

Beside the investigational product(s), the following study material will be supplied to the Phase I Unit:

- final version of the study protocol
- CRF for each subject plus some spare copies
- copy of the investigator's brochure (IB) relative to the IMPs
- informed consent forms

Moreover, before the start of the study, the investigator(s) will be provided with the following documents: ICH guidelines, confidentiality agreement (if applicable), protocol amendments (if any), declaration of Helsinki, insurance statement, SAE forms, financial agreement (if applicable), confidential subject identification code list form, drug accountability forms, investigator and study staff list form.

23.2 Protocol amendments

In order to obtain interpretable results, neither the Investigator nor the sponsor will alter the study conditions agreed upon and set out in this protocol with the only exception when immediate changes are necessary to protect the safety, rights, and welfare of the subjects. Amendments should be made by mutual agreement between the Investigator and the sponsor. Any amendment must be set out in writing, giving the reasons, and being signed by all concerned parties. The amendment becomes then part of the protocol. The study code, the title of the study, the progressive number and the date of the amendment must be recorded on the first page of the document. Exhaustive justifications that motivate the amendment to the protocol should clearly be addressed in the document.

All substantial amendments will be submitted to the concerned Regulatory Authorities, as applicable. The amendment(s)/modification(s) will be applicable only after approval, unless the changes consist of urgent safety measures to protect study subjects.

Non substantial amendments will be notified according to the current regulations.

In the event of an isolated, unforeseen instance resulting in a protocol deviation, the Investigator is to document this deviation and notify it to the CRO study project leader as soon as possible, in writing. In no instance should this increase the subject's risk or affect the validity of the study data.

23.3 Study documentation and record keeping

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

The Investigator must keep source documents for each subject in the study. All information on the CRFs must be traceable to these source documents, which are generally stored in the subject's medical file. The source documents should contain all demographic and medical information, including laboratory data, ECGs, etc., and the original signed informed consent forms.

Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The Investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects including lab tests and ECG tracing, insurance contracts, certificate of analysis of the IMP(s), drug accountability records, signed informed consent forms, confidential subjects identification code, CRFs, curricula vitae of the Investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final study report.

The Investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents. Should the Investigator or the CRO wish to assign the study documentation to another party or move to another location, the sponsor should promptly be notified.

All the essential study documents should be retained at the study site(s) in accordance to the applicable statutory terms and/or until the sponsor inform the Investigator/study site(s) in writing when the trial related records are no longer needed and in any case in accordance with FDA regulation 21 CFR 312.62(b) and (c) and ICH-GCP, national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

23.4 Study subjects' recruitment

Study participants will be recruited from the volunteers' database maintained by the CRO. This database contains a pool of volunteers that are contacted whenever necessary to enrol subjects in a new study. Before the start of the new study, the principal investigator and other relevant staff discuss with the volunteers' recruiter the study recruitment needs and specific requirements. On the basis of this information, the volunteers' recruiter queries the database, contacts potential participants to propose the study and evaluate their interest and availability. In addition to the volunteers' database, new subjects often call or email the CRO asking to become a research volunteer, after hearing of the clinical site activities from other volunteers or friends or after checking the company web site.

The CRO and its clinical site have detailed SOPs on the recruitment process.

23.5 Confidentiality and data protection

The Investigator shall keep secret from third parties any confidential information disclosed or provided by the sponsor, including but not limited to this protocol, CRF, and any other study information. Furthermore, prior to the study start-up, the CRO shall sign a confidentiality agreement with the Sponsor.

The processing of personal data of natural persons involved in the study is carried out in accordance with any applicable “Data Protection Laws", including without limitation the Swiss Federal Law on Data Protection (Law 235.1 of 19 June 1992 and subsequent updates), the Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of nature persons with regard to the processing of personal data and on the free movement of such data (hereinafter, GDPR”), as well as any other country regulations in that are similar, equivalent to or that are intended to or implement and/or modify the laws that are identified in above in relation to the protection of personal data. Both the controller and the processor are obliged to observe the rules and obligations coming from the applicable Data Protection Laws, as well as to set up the relevant processes for data subjects’ rights fulfilment. Each subject entering the study will be assigned a unique subject number (subject ID code) (see § 20.2). Any subject records or datasets that are transferred from the study site to the sponsor or to authorized vendors will be coded and will contain the subject ID code; subject names or any information which would make the subject identifiable will not be transferred. The Investigator must ensure that the subject’s confidentiality will be strictly maintained and that their identities are protected from unauthorized access. In order to respect the subject’s privacy, all the subject’s records, study reports, and communications, will identify the subject by the assigned unique subject ID code. The first two letters of the surname followed by the first two letters of the first name of the study subjects will be used in the Phase I Unit source document only and will not be transferred to the Sponsor. Laboratory specimens must be labelled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. The Investigator must keep a screening log showing the unique subjects’ numbers and associated names, for subjects screened and for all subjects enrolled in the trial. This log must be kept strictly confidential. The subject’s confidentiality will be maintained and will not be made publicly available, to the extent permitted by the applicable laws and regulations. The Sponsor of this study is the owner of all the data, information or material collected during the study according to the approved study protocol. Whether personal/coded or anonymous data are processed within the study, it will always be a protected information processing. Therefore, the CRO shall accept and implement appropriate technical and organizational security measures required by standard and regulations. The sponsor may transmit the personal data to recipients, such as sponsor, service providers and advisors and/or health authorities, located in third countries whose data protection laws may not offer equivalent protection only by taking all necessary steps to ensure the confidentiality, integrity and availability of personal data in accordance with applicable Data Protection Laws.

23.5.1 Subjects Personal Data Processing

Under the applicable Data Protection Laws, the sponsor, as well as the CRO and the Investigator are responsible for this study and will act as data controllers. Specifically, the Phase I Unit/CRO remains responsible when the Investigator uses uncoded subject data (or not coded) for medical or non-medical purposes. The controller of personal data, who determines the purposes and

means of processing within the overall study is the sponsor. The subject cannot be included in the study without a signed explicit informed consent form. The responsible for acquiring and storing of subject informed consent form is the Investigator/designee and/or the study site. The specific purposes of the study and of the data collection are described in the informed consent form, and information that the subject has been adequately notified about the processing of his/her data should be reported in the CRF. Medical records may be examined by the Quality Assurance Unit of the CRO in accordance with internal CRO procedures as well as by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. Further data processing in the study is in the coded regime, where the persons accessing any databases or registries based on their access rights are unable to identify the subject (directly or indirectly) without the use of additional information, as long as such additional information is kept separately and subject to technical and organizational measures to ensure non-attribution to an identified or identifiable individual. The Investigator is the contact person for the subject's rights fulfilment. The Investigator shall be familiarized with rules for personal data processing.

23.5.2 Investigator Personal Data Processing

The sponsor who receives information on Investigators, including sub-investigator(s) and study staff (directly or indirectly, through the CRO) is the Controller of the Investigators' personal data and the CRO is a Joint-Controller of the Investigators' personal data. The processors are other vendors (permitted sub-processors) managing the study. Within the study, the personal data of the Investigators are processed by the CRO and other authorized vendors on the basis of the creation of access accounts and communication during the study course. On the basis of a legitimate purpose, the Investigators data might be communicated to, and processed by the controllers or the processors (or permitted sub-processors) to ensure the smooth running of the study and high quality of collected data. In such a case, the investigators are properly informed about their data processing. Permitted sub-processors undertake to provide adequate notices to the Investigators (in a form provided by and on behalf of the sponsor/CRO) and undertake to ensure that all Investigators have acknowledged to the processing of their personal data as required for the following purposes: (a) the conduct of the study; (b) review by governmental or regulatory agencies, public authorities or pharmaceutical industries associations, CRO, the sponsor and its agents and affiliates; and (c) compliance with legal or regulatory requirements including those on disclosure of transfers of values from pharmaceutical companies to healthcare professionals and healthcare organizations; and (d) storage in databases for use in selecting study staff, and institutions for future clinical trials.

23.6 Future use of data

The personal information collected during this study (including any biological samples remaining at the end of the study), may also be added to research databases and used in the future by the sponsor and other companies and people working for or with the sponsor, for scientific research purposes to: (i) develop a better understanding of the safety and effectiveness of medicinal products; (ii) study other therapies for patients; (iii) develop a better understanding of diseases included in the Study; and (iv) improve the efficacy, design and methods of future studies. Personal information collected during this study may be stored and used for future research. The sponsor may agree on sharing upon request from qualified scientific and medical researchers anonymized individual subject-level data, study-level clinical trial data, and

protocols from clinical trials in patients for medicines and indications approved in the US and the EU, as necessary for conducting legitimate research. Medical researchers can request said data for new research.

23.7 Dissemination of Clinical Study Data

The sponsor is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. The sponsor assures that the key design elements of this protocol will be posted on a publicly accessible database, e.g., www.clinicaltrials.gov. In addition, results of this trial will be posted publicly according to local regulations. These posts (whether or not on the websites) will not include any information that allow identification of individual subjects.

- A clinical study report will be prepared and provided to the regulatory agency(ies), as appropriate. The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3 Guidance on CSR). Note that an abbreviated report may be prepared in certain cases.
- All data generated in this study required to be publicly available will follow all local and global regulations. Requests to delay submission of study results will follow the appropriate regulatory procedures, if warranted.
- Peer reviewed publication(s) of the study results will follow the publication policy detailed in section 23.8.

23.8 Publication policy

The sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the investigator publishing in peer reviewed journals, presenting results at scientific congresses and posting information and results on internet-based public registers and databases.
Study results will be communicated in full to the competent Health Authorities by the submission of a complete clinical study report.

As the sponsor agrees that the study results can be published by the investigator(s), the investigator agrees to submit any manuscript (abstract, publication, paper, etc.) to the sponsor before any public disclosure.
This will be done in order to ensure that clinical study results are reported in an objective, accurate and balanced manner. The sponsor reviews the proposed manuscripts, before submission, within a reasonable period of time (30-90 days in relation with the complexity of the work).

The investigator will also be provided by the sponsor with the clinical study report and the results of any additional analysis, tables, figures, etc. undertaken for the purposes of the article, in order to take responsibility for the content of the publication(s).
On an exceptional basis, the sponsor may temporarily delay registration of certain data elements (e.g., compound, name, outcome, measures, etc.) to seek necessary intellectual property

protection. This is because early disclosure of such data could, in some circumstances, prevent or negatively impact patentability.

According to The Federal Act on Research involving Human Beings and the Ordinance on Clinical Trials in Human Research, the study will be registered and published in a WHO primary register or clinicaltrials.gov as well as in the supplementary federal database.

24 REFERENCES

1. Grunberg SM. Overview of chemotherapy-induced nausea and vomiting. Clin Adv Hematol Oncol. 2013;11(2 suppl 1):1-18
2. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008;358(23):2482-94
3. Rojas C, Raje M, Tsukamoto T, Slusher BS. Molecular mechanisms of 5-HT3 and NK1 receptor antagonists in prevention of emesis. Eur J Pharmacol. 2014;722:26-37
4. IV Fosnetupitant 235 mg/ Palonosetron 0.25 mg infusion, Investigator's Brochure
5. IV Fosnetupitant 235 mg, Investigator's Brochure
6. Bittner B and Mountfield R. Intravenous administration of poorly soluble new drug entities in early drug discovery: the potential impact of formulation on pharmacokinetic parameters. Curr Opin Drug Discov Devel 2002;5:59-71
7. Guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4
8. Ottoboni T, Lauw M, K MR, Cravets M, Manhard K, Clendeninn N and B Quart. HTX-019 via 2-min injection or 30-min infusion in healthy subjects. Future Oncol. 2019;15(8):865-874
9. Guidance for Industry. Bioavailability Studies Submitted in NDAs or INDs — General Considerations. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Apr 2022
10. Kurteva G, Chilingirova N, Rizzi G, Caccia T, Stella V and A Bernareggi. Pharmacokinetic profile and safety of intravenous NEPA, a fixed combination of fosnetupitant and palonosetron, in cancer patients: Prevention of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy. European Journal of Pharmaceutical Sciences 2019;139:105041
11. U.S. Department of Health and Human Services and U.S. Department of Agriculture, Nutrition and your health: 2020-2025 Dietary Guidelines, Appendix 9
12. OECD, OECD. Principles of Good Laboratory Practice ENV/MC/CHEM (98) 17. 1998
13. SAS/STAT® User's Guide
14. WinNonLin Getting Started Guide, Pharsight Corporation
15. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH – Efficacy Topic 6(R2): Guideline for Good Clinical Practice, EMA/CHMP/ICH/135/1995, Dec 2016
16. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH – Efficacy Topic E2A: Clinical Safety Data Management: Definition and Standards for Expedite reporting, 27 Oct 1994