CLINICAL STUDY PROTOCOL

A RANDOMIZED, SINGLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFECTS OF REPEAT DOSES OF NT-814 ON ESTRADIOL AND OTHER SEX HORMONE CONCENTRATIONS IN HEALTHY PRE-MENOPAUSAL FEMALE VOLUNTEERS

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Sponsor:	NeRRe Therapeutics Ltd, Stevenage Bioscience Catalyst, Gunnels Wood Road, Stevenage, SG1 2FX, United Kingdom
SAE Reporting:	Emas Pharma Pharmacovigilance Tel.: +44 1462 424416 Fax: +44 1462 600456 Email: Drug.Safety@bionical-emas.com

Confidentiality Statement:

This protocol contains information which is the property of NeRRe Therapeutics Ltd and therefore is provided to you in confidence for review by you, your staff, an applicable ethics committee/institutional review board and regulatory authorities. It is understood that this information will not be disclosed to others without the written approval from NeRRe Therapeutics Ltd.

This study will be conducted in compliance with Good Clinical Practice (GCP), the General Principles of the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

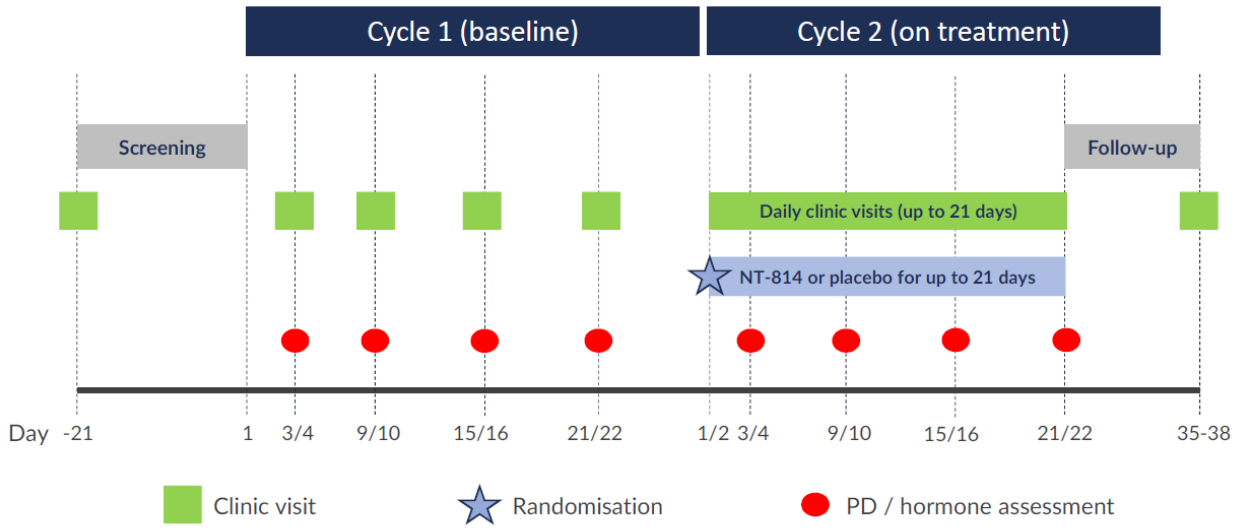
1 PROTOCOL SYNOPSIS

Protocol Title	**A randomized, single-blind, placebo-controlled study of the effects of repeat doses of NT-814 on estradiol and other sex hormone concentrations in healthy pre-menopausal female volunteers**
Protocol Number	814-1-05
Sponsor	NeRRe Therapeutics Ltd
Investigational Product	NT-814
Study Phase	Phase 1
Indication	Not applicable

Study Objectives and Endpoints	
Objectives	**Endpoints/Study Outcomes**
Primary	
To determine the effects of NT-814 given at doses of 40 mg, 80 mg, 120 mg, and 160 mg once daily for approximately 21 days on GnRH pathway hormones in healthy female subjects	• Change from baseline in serum LH, FSH, estradiol and progesterone over a full menstrual cycle
Secondary	
To evaluate the safety of NT-814	• 12-lead ECGs: abnormalities; change from baseline in quantitative parameters (RR interval, PR interval, QRS duration, absolute QT interval and QTcF) • Change from baseline in clinical laboratory assessments (hematology, biochemistry) • Change from baseline in vital signs (BP, pulse rate, weight) • Nature and severity of TEAE; withdrawals due to TEAE
Exploratory	
To evaluate the pharmacokinetic-pharmacodynamic (PK-PD) relationship of NT-814	• NT-814 plasma concentrations concurrent with serum LH, FSH, estradiol and progesterone during Cycle 2

Study Design	Randomized, single-blind, placebo-controlled, parallel group study of up to four NT-814 dose levels (40, 80, 120 and 160 mg) and placebo. The study includes an assessment of hormone concentrations during a baseline menstrual cycle.

	The study will consist of two cohorts, with the second cohort being optional depending on the pharmacodynamic response observed in Cohort 1. Cohort 1 will consist of 32 subjects randomized to receive NT-814 40mg, 80mg, 120mg or placebo once daily for up to 21 days in parallel groups, 8 subjects in each group. After Cohort 1 complete Cycle 2, the pharmacodynamic data will be assessed and a decision made as to whether to study an additional dose of 160mg daily NT-814. In the case that any subjects in Cohort 1 withdraw or are withdrawn from the study prior to completion of Cycle 2 they will be replaced at the discretion of the Sponsor. If the 160mg dose is to be assessed, an additional Cohort 2 will be enrolled – consisting of 10 subjects randomized to receive either NT-814 160mg (8 subjects) or placebo (2 subjects) daily.
Study Methodology	Subjects will participate in the study during two consecutive menstrual cycles. After obtaining written informed consent, each subject will undergo screening procedures within 21 days before the anticipated start of the baseline assessment cycle (Cycle 1). Eligible subjects will first attend the study unit on either Day 3 or 4 of Cycle 1 (where Day 1 is the first day of menstruation). Blood samples will be collected for measurement of hormones (estradiol, progesterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH). Subjects will return to the study unit for a further three out-patient visits on Day 9 or 10, Day 15 or 16, and Day 21 or 22. Blood samples for serum hormones will be collected at each visit. At the clinic visit on Day 21 or 22, subjects will additionally have safety assessments performed. Subjects will return to the study unit either the day of or the day following (or, in exceptional circumstances, 2 days following) the first day of their next menstrual cycle and after completion of baseline safety assessments will be randomized to study treatment; they then will receive their first dose of study medication. They will attend the study unit daily in the morning for a further 20 days to receive their study medication (for a total of up to 21 days treatment). Additionally, on Day 3 or 4, Day 9 or 10, Day 15 or 16, and Day 21 or 22, blood samples for serum hormones and plasma levels of NT-814 will be collected. The sampling days relative to Day 1 of Cycle 2 will match the days samples were taken in Cycle 1 (relative to Day 1 of Cycle 1) within each subject. Out-patient visits are to occur in the morning and should occur at approximately the same time of day throughout Cycle 2, and approximately the same time of day as the visits in Cycle 1. Safety will be monitored throughout the study with routine safety assessments (adverse event (AE) recording; vital signs; 12-lead ECG; clinical laboratory tests). A physical examination will be conducted at

	screen and follow-up. Additional safety assessments will be done at any time as considered appropriate by the Investigator. Subjects will have a final outpatient follow-up visit two weeks following the final dose of study medication.
The study schematic is shown.  	
Planned Sample Size & Statistical Considerations	The initial cohort will comprise 32 subjects, eight in each of the three NT-814 and placebo groups. If the high (160 mg) dose of NT-814 is evaluated, an additional 10 subjects will be recruited, eight subjects randomized to the NT-814 group and two to the placebo group. Placebo subjects will be pooled in the final analyses. Subjects who do not complete the study may be replaced. A maximum of 10 additional subjects to replace subjects who withdraw may also be enrolled. Thus, the total sample size will be 32 completed subjects if three doses of NT-814 are evaluated and will be 42 if four doses are evaluated. No formal sample size assessment has been conducted but this sample size is typical of exploratory mechanistic studies and is considered sufficient for the objectives of the study to be achieved.
Subject Population	Healthy pre-menopausal female volunteers

Key Inclusion Criteria	• Healthy, female, aged 18 to 45 years inclusive (age at time of informed consent) • Regular (approximately) monthly menstrual periods • Able and willing to understand and comply with the requirements of the study and give written informed consent • Body mass index in the range 18.0 to 32.0 kg/m^2 and body weight not less than 40.0 kg • Judged to be in good health, based on the results of medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory findings • Not pregnant and not lactating, with no intention of pregnancy during study treatment • Agree to use two acceptable methods of birth-control, one of which is a barrier method with spermicide[1] for the duration of participation in the study and 30 days after the last dose of study medication
Key Exclusion Criteria	• Previous participation in this or any other study of NT-814 • Have taken any prescription or nonprescription drug, vitamin, dietary supplement and/or herbal supplement that is a strong inducer of cytochrome P450 metabolizing enzymes within 1 month, or any prescription or nonprescription drug, vitamin, dietary supplement and/or herbal supplement within 1 week (or 5 half-lives, if longer) before the first dose of study medication, with the exception of acetaminophen (paracetamol) at doses up to 2100 mg/day. • Any medication which will alter endogenous hormone levels especially hormonal contraceptives (given by any route) • Previous bilateral oophorectomy and/or hysterectomy

1 Acceptable methods of birth control are surgical sterilization of the subject's male partner, if he is the sole partner of that subject; surgical sterilization by bilateral tubal ligation, a non-hormonal intrauterine device (IUD) inserted at least one month before study drug administration and to remain in place for at least 30 days after the last dose of study drug; barrier methods such as male condom or cap, diaphragm or sponge with spermicide. An exclusively homosexual or abstinent lifestyle s also acceptable, provided it is maintained throughout the duration of the study and for 30 days afterwards.

Study Drug	NT-814 will be provided as 40-mg soft-gel capsules and placebo to match, for oral administration. All subjects will receive 4 capsules per day, with placebo capsules being used to make up the count in subjects randomized to doses lower than 160 mg. Dose — IMP Supply Placebo: 4 x placebo capsules 40 mg: 1 x NT-814 capsule + 3 x placebo capsules 80 mg: 2 x NT-814 capsule + 2 x placebo capsules 120 mg: 3 x NT-814 capsule + 1 x placebo capsules 160 mg: 4 x NT-814 capsule Doses will be prepared in the clinic and subjects will attend the clinic in the morning each day during dosing to take the study medication, starting on Day 1 or 2 (or exceptionally Day 3) of Cycle 2. The total duration of treatment will be up to 21 days.
Pharmacodynamic (hormone) Assessments	• Blood samples will be collected for measurement of serum estradiol, LH, FSH and progesterone.
Safety Assessments	Safety and tolerability will be assessed by the following: • Vital signs (supine BP, pulse rate, weight) • 12-lead ECGs • Clinical laboratory assessments (hematology, biochemistry) • Adverse events
Pharmacokinetic assessments	• Blood samples will be collected for measurement of plasma levels of NT-814.

Statistical Methods	All PD, PK and safety data will be listed and summarized by treatment and time point using appropriate descriptive statistics including change from baseline as appropriate. The safety and tolerability profile will be assessed versus baseline conditions. The pharmacodynamic data (i.e. LH, FSH, estradiol and progesterone) in Cycle 2 will be assessed versus baseline (Cycle 1), and descriptive statistics for change from baseline will be produced, where applicable. The changes from baseline will be analyzed using a fixed effects model with treatment as a fixed effect and the corresponding baseline value as a covariate. The adjusted arithmetic means from the model for the changes from baseline including 95% confidence interval (CI) will be presented for each treatment. In addition, the following comparisons will be performed and the difference in the adjusted arithmetic means and 90% CI will be presented: • each dose level of NT-814 vs placebo This analysis will be performed for each day separately (i.e. Days 3/4, 9/10, 15/16 and 21/22). A repeated measures analysis may be used if considered appropriate. Plasma concentrations of NT-814 will be summarized descriptively; possible exposure-response relationships will be explored.
Abbreviations: BP: blood pressure; ECG: electrocardiogram; FSH: follicle stimulating hormone; GnRH: gonadotrophin releasing hormone; LH: luteinizing hormone; PK: pharmacokinetic; PD: pharmacodynamic; QTcF: QT interval corrected for heart rate using Fridericia's correction; TEAE: treatment-emergent adverse event	

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2 ABBREVIATIONS AND DEFINITIONS

ADR	Adverse drug reaction
AE	Adverse event
anti-HBc	Hepatitis B core antibody
AUC	Area under the concentration versus time curve over the specified periods
AUC_{inf}	AUC from time of dosing extrapolated to infinity
BMI	Body mass index
BP	Blood pressure
C_{last}	Last quantifiable concentration
C_{max}	Maximum concentration
CRO	Contract research organization
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DHEA	Dehydroepiandrosterone
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	(US) Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotrophin releasing hormone
GSK1144814	Former laboratory code name for NT-814[1]
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
IRB	Institutional Review Board
IUD	Intra-uterine (contraceptive) device
IUS	Intra-uterine (contraceptive) system
LC-MS/MS	Liquid Chromatography – Mass Spectrometry analytical methodology
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
NK	Neurokinin
PET	Positron emission tomography
PK	Pharmacokinetic
QTcF	QT interval corrected for heart rate using Fridericia's correction, $QTcF=QT/RR^{⅓}$
RAP	Reporting and Analysis Plan
SAE	Serious adverse event
SBP	Systolic blood pressure

[1] The GSK laboratory code (GSK1144814) may be used in this and other trial related document when referring to studies conducted by GSK. NT-814 is used for all development activities conducted by NeRRe as Sponsor

SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
SI	Système International
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time after dosing of occurrence of C_{max}
US	United States (of America)
WHO	World Health Organisation

3 INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

KaNDy Therapeutics Ltd has delegated all regulatory and quality Sponsor responsibilities to NeRRe.

Principal Investigator and Affiliations	Maricer Escalon, MD MA MBA Quotient Sciences 3898 N.W. 7th Street Miami, Florida 33126 United States (US) Tel: +1 305 644 9903 e-mail: maricer.escalon@quotientsciences.com
Contract Research Organization	Quotient Sciences 3898 N.W. 7th Street Miami, Florida 33126 United States (US) Tel: +1 305 644 9903
Medical Monitor (Sponsor)	Kirsteen Donaldson, DM FRCP FFPM Jade Consultants (Cambridge) Ltd xxxxxxxxx xxxxxxxxxx xxxxxxxxxx United Kingdom Tel: +44 xxxx xxxxx (home/office) Cell: +44 xxxx xxxxxx email: xxxxx@xxxxxxxxx.co.uk
Pharmacovigilance Provider	Emas Pharma 63-56 Knowl Piece Wilbury Way Hitchin, SG4 0TY United Kingdom Tel: +44 1462 426488 Fax: +44 1462 424426 Email: rukhnoor.mahmood@bionical-emas.com
Clinical Laboratory (safety)	Seaview Labs SeaView Research Inc., 3898 N.W. 7th Street Miami, Florida 33126 United States (US) Tel: +1 305 631 6066

Clinical Laboratory (PD hormones)	Quest Diagnostics 4225 East Fowler Avenue, Tampa, Florida 33617 United States (US) Tel: +1 813 972 7100 Quest Diagnostics Nichols Institute 33608 Ortega Highway San Juan Capistrano, California 92675 United States (US) Tel: +1 949 728 4000

4 INTRODUCTION

4.1 Rationale for this Study

Sex hormone levels and reproduction organ function in both men and women are controlled by gonadotropin-release hormone (GnRH). The hypothalamus releases GnRH and it, in turn, stimulates the secretion of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. GnRH is released in a pulsatile manner with the frequency of the pulses regulating the release of LH and FSH and hence sex hormone production in the gonads.

Endometriosis is a chronic condition affecting up to 10% of women of reproductive age. It results in endometrial tissue implanting outside the uterus causing symptoms such as dysmenorrhea, lower abdominal pain, pain at ovulation, dyspareunia, constipation and dysuria[1,2,3]. The condition is estrogen dependent with the hormone causing extra-uterine implantation and proliferation of endometrial tissue, and also local and systemic inflammation. The chronic nature of the condition along with the associated symptoms can severely affect the subject's quality of life along with their intimate relationships[4,5,6].

Fibroids (uterine leiomyomas) are very common, occurring in 50–60% of women, rising to 70% by the age of 50 [7,8]. It is a benign condition which is symptomatic in up to 50 % of cases[9,10]. As with endometriosis, the symptoms such as lower abdominal pain, prolonged and heavy vaginal bleeding, and dysmenorrhea can all severely impact a subject's quality of life[11] and lead to a significant economic burden.

The etiology of uterine leiomyomas remains unclear but as leiomyomas rarely occur before menarche and usually regress after menopause it is thought that the sex hormones may have a role.

The fact that both endometriosis and uterine leiomyomas appear to be, to a certain degree, estrogen dependent, is used in their treatment, where both GnRH agonists and antagonists have been used to decrease the plasma estradiol levels[12,13,14]. However, treatment with GnRH agonists and antagonists can reduce hormone levels to postmenopausal levels which can lead to bone loss and hot flushes which can result in a shortened duration of treatment or the need for hormone replacement therapy[15,16,17].

Barbieri[18] has suggested that different tissues may have different responsiveness to estrogen. This opens up the possibility of being able to reduce plasma levels to a concentration which is low enough to inhibit drive to aberrant tissue but not so low as to cause the problems associated with postmenopausal levels.

Recent evidence suggests that neurokinin B (NK-B) is needed for the effective functioning of the reproductive system in both men and women, through modulation of gonadotrophin-releasing hormone (GnRH). This is evidenced by genetic mutations leading to hypogonadotropic pubertal delay due to the loss of NK-B (TAC3) and its receptor (TAC3R)[19].

The effect of NK-B in smaller animal species is mixed, with both inhibitory and stimulatory effects being seen in rodent models[20,21,22,23]. In larger animals such as goats, sheep and monkeys, however, more conclusive evidence of a stimulatory effect on LH is seen[24,25,26,27].

Similarly, the administration of neurokinin-3 (NK_3) receptor antagonists (NK3Ra) has provided evidence of the involvement of this pathway in both human and animal reproduction through the regulation of GnRH secretion.

Systemic administration of an NK_3 antagonist (ESN364) was shown to extend the interpulse interval in LH in gonadectomized ewes and was also shown to lower the plasma concentrations of LH and FSH

in castrated nonhuman primates (Macaca fascicularis). Importantly, daily oral dosing of ESN364 for the duration of the menstrual cycle in M fascicularis lowered plasma estradiol levels in a dose-dependent manner, but levels of estradiol were maintained well above menopausal levels throughout[28].

Another NK_3 antagonist, MLE4901, also led to a decrease in LH concentrations and a prolongation of the LH interpulse interval in healthy women during estrogen administration[29], and in women with polycystic ovary syndrome (PCOS)[30].

In another study, MLE4901 was given to healthy women for 7 days, starting during the follicular phase of their cycle. This led to reduced basal LH secretion (without change in the pulse frequency), delay in the LH surge, and prevention of both follicle growth and of increase in estradiol concentrations. On withdrawal of treatment, follicle development resumed and oestradiol concentrations normalized[31].

Fraser et al showed that 21 days' treatment in regularly cycling women with ESN364 resulted in decreases in LH but not FSH. This led to decreases in estradiol and progesterone causing delay in ovulation, decreased endometrial thickening, slowed follicular maturation and an extended cycle[32].

Taken together, the evidence suggests that NK antagonists might selectively reduce LH levels but not FSH due to modulation of the GnRH pulse frequency. This reduces level of ovarian hormones but not to a level that would lead to adverse events associated with post-menopausal hormone levels. Along with an acceptable safety profile, this raises the potential of NK antagonists to be used in the treatment of uterine fibroids and endometriosis.

4.2 Non-clinical Information

4.2.1 Pharmacology Relevant to Mode of Action

In vitro binding and functional studies have demonstrated that NT-814 is a potent and selective antagonist of both NK_1 and NK_3 receptors. NT-814 is active in a dose-dependent manner in pharmacodynamic models for the NK_1 receptor (the gerbil foot tapping test) and NK_3 receptor (wet dog shaking behavior in guinea pigs). NT-814 also shows non-sedating anxiolytic-like properties in the human threat test in the marmoset.

The brain-penetrant properties of NT-814 have been confirmed *in vivo* in the gerbil, in which sustained dose- and concentration-dependent occupancy was shown at both brain NK_1 and NK_3 receptors. NT-814 also occupied guinea pig striatal NK_1 receptors and cortical NK_3 receptors in a dose- and concentration-dependent manner. In a positron emission tomography (PET) study in baboons, NT-814 achieved high NK_1 receptor occupancy at modest plasma concentrations.

4.2.2 Off-target Pharmacology, Safety and Toxicology

NT-814 was >100-fold selective for the human NK_3 receptor and >300-fold for the human NK_1 receptor, in comparison with 53 other non-tachykinin receptors, ion channels, enzymes and transporters.

There were no clinically relevant findings in respiratory or neurobehavioral safety pharmacology studies at doses up to 100 mg/kg or in a cardiovascular study in cynomolgus monkeys at doses up to 60 mg/kg. NT-814 did not inhibit human ether-à-go-go related gene (hERG) tail current at concentrations up to 1.9 μM.

A full package of non-clinical safety studies appropriate to the stage of development has been completed with NT-814. This includes single-dose studies in marmoset and monkey (up to

1000 mg/kg) and repeat-dose studies of up to 13-weeks in rat (up to 100 mg/kg/day) and cynomolgus monkey (up to 40 mg/kg/day). No specific target organ toxicity was identified in either species. Adverse findings in the renal, gastrointestinal and cardiovascular systems in the 4-week studies are considered to be secondary to inappetence and dehydration as a result of the high local drug load, resulting in local gastric irritancy and toxicity. In general, the findings indicated an acceptable safety profile that did not preclude entry into clinical studies with appropriate monitoring.

4.3 Clinical Experience

Eight clinical studies have been completed with NT-814, seven in healthy volunteers and one in female patients with troublesome post-menopausal symptoms (hot flashes). In addition, an investigator-initiated study in opiate-use disorder was terminated after enrolling five subjects after it was determined that the study could not fulfil its objectives for PK reasons. In total, more than 230 healthy volunteers and patients have received NT-814 on at least one occasion, including 134 subjects who have been given repeat doses for between 5 and 28 days.

Healthy volunteer studies comprised single- and multiple-escalating-dose and repeat dose safety studies, both with an evaluation of receptor occupancy by PET, a single-dose study assessing the PK and effect of food on exposure to a tablet formulation of NT-814, a single-dose study assessing whether the psychomotor and cognitive effects of alcohol are exacerbated by NT-814, a relative bioavailability study comparing two NT-814 formulations, a repeat dose study with a soft-gel formulation, and various drug-interaction assessments. In total, approximately 200 subjects participated in these healthy volunteer studies, of which 190 received at least one dose of NT-814.

In addition, 76 female subjects with post-menopausal symptoms took part in the RELENT-1 study and received once daily treatment with NT-814 or placebo for 14 days. Five male subjects participated in the opiate use disorder study of which four received NT-814 for 14 days in a cross-over design.

A placebo-controlled study of NT-814 (at doses of 40, 80, 120 and 160 mg once daily) in up to 165 female subjects with moderate to severe post-menopausal hot flashes is currently ongoing (Study 814-PM-02).

4.3.1 Pharmacokinetics and Pharmacodynamics

Following single oral doses of a suspension formulation of the tosylate salt of NT-814 in healthy male volunteers, the PK were characterized by rapid and extensive absorption, with peak NT-814 concentrations generally observed approximately 1 hour after dosing. Systemic exposure to NT-814 increased in a slightly greater than proportional manner. The terminal elimination half-life (t1/2) was estimated to be 15 to 18 hours. Following repeated oral doses of a suspension formulation of the tosylate salt of NT-814 in healthy male volunteers, steady state was achieved by Day 5. The increases in exposure with increased dose were slightly greater than dose-proportional and the t1/2 was estimated to be approximately 22 hours.

After oral doses of NT-814 free base in a hard-gel capsule formulation in post-menopausal females, exposure increased proportionately over the dose range 50 to 300 mg. However, exposures varied widely, both within and between subjects, with this formulation. Steady state was achieved by Day 7, accumulation was modest (generally less than 2-fold) and the t1/2 was estimated to be 20-22 hours.

Compared to the hard-gel formulation, the lipidic soft-gel formulation of NT-814 had reduced between-subject variability. Within the comparative bioavailability study, the dose-corrected exposure from the soft-gel formulation was similar to that achieved with the hard-gel formulation. However,

NT-814 was approximately twice as bioavailable when compared to the exposures observed in females in the RELENT-1 study using the hard-gel formulation. The soft-gel formulation is the current development form of NT-814 and will be used in the present study.

There was no effect of food on the AUC extrapolated to infinity (AUC_{inf}) after single doses of NT-814 given as a tablet formulation of the free base and a modest (9%) reduction in AUC with a 25 mg dose in the soft-gel capsule formulation. Administration with food did, however, reduce the maximum concentration (C_{max}) by approximately 36% with the tablet formulation and 71% with the soft-gel capsule formulation. With both formulations, the time after dosing of C_{max} (T_{max}) was delayed (to between 2.5 and 3.5 hours) by food.

In PET studies using radiolabelled NT-814, the plasma concentrations associated with 50% and 95% brain NK_1 receptor occupancy (EC_{50} and EC_{95}) were approximately 0.9 ng/mL and 19 ng/mL, respectively. It is not possible to assess NK_3 receptor occupancy directly as a suitable NK_3 PET ligand does not exist. Based on the 5 to 10-fold lower affinity for NK_3 receptors as compared to NK_1 receptors, the EC_{95} for NK_3 receptor occupancy is estimated to be in the range 95 to 190 ng/mL.

Testosterone concentrations reduced in an approximately dose-dependent manner in male subjects receiving higher single and repeat doses of NT-814. In female subjects participating in the RELENT-1 study, there were small reductions from baseline in luteinizing hormone concentrations on the first day of treatment with higher NT-814 doses. These findings are expected pharmacodynamic responses to NK_3 (and possibly NK_1) antagonism and are considered evidence of target engagement.

4.3.2 Safety and Tolerability

NT-814 has been well tolerated both after single and repeat doses. All reported adverse events (AE) have been transient and mild or moderate in severity; no treatment-related serious adverse events (SAE) have been observed. One subject in the opiate-use disorder study died after completing the study from an unrelated drug overdose. Non-serious AEs considered related to treatment with NT-814 are headache, diarrhea and somnolence.

No treatment-related effects on electrocardiogram (ECG) parameters, vital signs or routine safety laboratory testing have been observed. Extended continuous Holter ECG monitoring in the RELENT-1 study did not identify any treatment-related effect on heart rhythm.

Further information on the pre-clinical and clinical studies undertaken with NT-814 can be found in the current version of the Investigator's Brochure (IB)[33].

4.4 Study Design Considerations

This is a standard study design for assessing the effect of different doses on the serum concentrations of various hormones. It is sufficient for just the subject to be blinded to treatment as there are no subjective efficacy elements being measured in the study but blinding subjects to treatment potentially reduces bias in the reporting of safety findings. The doses proposed in this study are currently being studied in women with hot-flashes associated with the menopause. The proposed duration of treatment and number of subjects per treatment arm are considered sufficient to adequately assess the effect of NT-814 on the hormones under study.

4.5 Risks and Risk Mitigation

4.5.1 Risks to Study Subjects

As NT-814 is still in the early stages of development and its effects on the developing fetus or neonate have not been fully evaluated, pregnant or breast-feeding women must not be given NT-814. NT-814 was not genotoxic. At a dose of 100 mg/kg/day there were increased pre- and post-implantation embryo losses, reduced litter size and reduced embryo weights in fertility studies in rats. However, there was no evidence of fetal abnormalities in either rats or rabbits and there was no evidence of embryofetal toxicity in the rat at doses up to 100 mg/kg/day or in the rabbit at doses up to 140 mg/kg/day.

Subjects must be using non-hormonal birth control. Accordingly, whilst 'highly effective' birth control (one with a failure rate less than 1% per annum) is desirable, it is considered that two "acceptable" methods of birth control, one of which must be a barrier method with spermicide, is also appropriate for this study[34]. Acceptable methods of contraception are listed in Section 8.8.2. Hormonal contraception by any route (including a progestin-releasing intrauterine system, IUS) is not acceptable for this study since it is likely to affect the pharmacodynamic endpoints of the study. Subjects who have undergone bilateral oophorectomy will be excluded since this will also affect the pharmacodynamic endpoints, and subjects who have undergone hysterectomy will be excluded because of the difficulty in recognizing the first day of menstruation in each cycle.

Subjects who are allergic to NT-814 or any of the excipients in the formulation will be excluded.

Full lists of subject inclusion and exclusion criteria are provided in Sections 7.2.

A study of photochemical properties showed that NT-814 absorbs photons in the visible part of the light spectrum and there was a positive finding in an *in vitro* phototoxicity study. The relevance of these findings is unclear. Although recommended by regulatory guidelines, the *in vitro* study has a high false-positive rate and, despite subjects in clinical studies not being required to take precautions with respect to sunlight, there have been no adverse events consistent with clinical phototoxicity. Investigators and subjects are advised to be vigilant to the occurrence of sunburn-like skin reactions and to avoid direct exposure to strong sunlight should this occur.

In general, treatment-with NT-814 has been well-tolerated in clinical studies. However, attention is drawn to the following safety information.

Several subjects participating in phase 1 studies with NT-814 were noted to have cardiac arrhythmias coincident with their participation in the studies. However, there were no findings in the pre-clinical safety studies that would suggest that NT-814 is pro-arrhythmic, and extensive Holter monitoring in the RELENT-1 study did not identify any difference between placebo and NT-814 in the incidence of arrhythmias. Nonetheless, subjects participating in studies should undergo periodic ECG evaluation, either as required by the protocol or indicated clinically.

Mild somnolence has been reported at a higher incidence in subjects receiving higher doses of NT-814. Subjects who experience somnolence should avoid driving or use of machinery.

No serious or severe adverse reactions are considered expected with NT-814. Expected adverse reactions comprise moderate headache, mild somnolence, and mild diarrhea.

Another NK_1 antagonist has recently been reported to be linked with clinically significant elevations in liver enzymes. Small (not clinically significant) rises in LFTs in subjects taking NT-814 have been

reported in the RELENT-1 study but at a lower frequency than in subjects taking placebo in that study. A subject in the ongoing (and still blinded) vasomotor symptom study was withdrawn from treatment because of elevated transaminases. Subjects participating in studies should have their LFTs monitored regularly for any unexpected rises.

4.5.2 Potential for Drug-Drug Interaction

Plasma protein binding of NT-814 was very high (greater than 99.5% in all species tested).

In vivo (rat and monkey), elimination of NT-814 was mainly by metabolism. The predominant human metabolic pathway appears to be oxidation by cytochrome P450 (CYP) 3A4. Based on a clinical interaction study with midazolam, NT-814 is also a weak inhibitor of CYP3A4.

In vitro data indicate that NT-814 is a substrate and weak inhibitor of human P-glycoprotein (P-gp). It is also a moderate inhibitor of human organic anion transporting polypeptide 1B1 and a weak inhibitor of human breast cancer resistance protein. Preliminary data from a human clinical interaction study with itraconazole indicates that NT-814 is a moderately sensitive substrate of CYP3A4 and/or P-gp.

In this study, subjects will be excluded if they are taking, or are likely to need to take, non-study medication other than low doses of paracetamol (acetaminophen) (see Section 8.8.1). The potential risk of drug-drug interaction will be taken into account in selecting concomitant medication to treat an emergent adverse event. If concomitant medication needed to treat AEs is likely to be associated with increased risk to the subject or to reduce the likelihood of achieving the study objectives, the subject should discontinue dosing with study medication and/or be withdrawn from the study (see Section 7.4).

5 STUDY OBJECTIVES AND CORRESPONDING ENDPOINTS

The study objectives and corresponding endpoints/study outcomes are presented in Table 5-1.

Table 5-1 Objectives and Corresponding Endpoints/Study Outcomes

Objectives	Endpoints/Study Outcomes
Primary	
To determine the effects of NT-814 given at doses of 40 mg, 80 mg, 120 mg, and 160 mg once daily for approximately 21 days on GnRH pathway hormones in healthy female subjects	• Change from baseline in serum LH, FSH, estradiol and progesterone over a full menstrual cycle
Secondary	
To evaluate the safety of NT-814	• 12-lead ECGs: abnormalities; change from baseline in quantitative parameters (RR interval, PR interval, QRS duration, absolute QT interval and QTcF) • Change from baseline in clinical laboratory assessments (hematology, biochemistry) • Change from baseline in vital signs (BP, pulse rate, weight) • Nature and severity of TEAE; withdrawals due to TEAE
Exploratory	
To evaluate the pharmacokinetic-pharmacodynamic (PK-PD) relationship of NT-814	• NT-814 plasma concentration levels concurrent with serum LH, FSH, estradiol and progesterone during Cycle 2
To evaluate the effect of NT-814 on menstrual cycle length	• Change from baseline (Cycle 1) in the length of the menstrual cycle

6 STUDY DESIGN

The study uses a randomized, single-blind, placebo-controlled design. The study will consist of two cohorts, with the second cohort being optional depending on the pharmacodynamic (hormonal) response observed in Cohort 1.

Cohort 1 will consist of 32 subjects randomized to receive NT-814 40mg, 80mg, 120mg or placebo once daily in parallel groups, 8 subjects in each group. After Cohort 1 complete Cycle 2, the pharmacodynamic data will be assessed by a team comprising of the Sponsor medical representative, Sponsor medical expert, Investigator and statistician. If a maximal response (estradiol reduction) is not observed at the lower doses the higher dose of 160 mg dose will be assessed. A maximal response will be considered as having been achieved if the response observed at 120 mg is not meaningfully greater than that observed at 80 mg. In the case that any subjects in Cohort 1 withdraw or are withdrawn from the study prior to completion of Cycle 2 they will be replaced at the discretion of the Sponsor.

If the 160mg dose is to be assessed an additional Cohort 2 will be enrolled – consisting of 10 subjects randomized to receive either NT-814 160mg (8 subjects) or placebo (2 subjects).

Subjects will participate in the study during two consecutive menstrual cycles.

After obtaining written informed consent, each subject will undergo screening procedures within 21 days before the anticipated start of the baseline assessment cycle (Cycle 1).

Eligible subjects will first attend the study unit on the morning of either Day 3 or 4 of Cycle 1 (where Day 1 is the first day of menstruation) for the start of the baseline assessment cycle. Blood samples will be collected for measurement of hormones (estradiol, progesterone, LH, and FSH).

Subjects will return to the study unit for a further three out-patient visits on the mornings of Day 9 or 10, Day 15 or 16, and Day 21 or 22. Blood samples for serum hormones will be collected at each visit. Samples for serum hormone assessment must be taken at the same time of day on all days (±1hr).

At the clinic visit on Day 21 or 22, subjects will additionally have safety assessments performed.

Subjects will return to the study unit in the morning of either the day of or the day following (or, in exceptional circumstances, 2 days following) the first day of their next menstrual cycle (the first day of bleeding; Cycle 2) and, after completion of baseline safety assessments, will be randomized to study treatment; they will then receive their first dose of study medication. They will attend the study unit daily in the morning for up to 20 further days to receive their study medication (so a total of up to 21 days dosing) with the last dose to be taken on the day prior to the Day 21 or 22 visit.

Additionally, on Day 3 or 4, Day 9 or 10, Day 15 or 16, and Day 21 or 22, blood samples for serum hormones will be collected and a single sample for measurement of plasma levels of NT-814 will also be collected. Blood samples for serum hormones (and PK) must be taken at the same time of day as the hormone samples were taken in Cycle 1 (±1hr).

The serum hormone sampling days relative to Day 1 of Cycle 2 will match the days samples were taken in Cycle 1 (relative to Day 1 of Cycle 1) within each subject (e.g. if the subject attended the clinic on Day 4 in Cycle 1, the hormone sample must be taken on Day 4 in Cycle 2; if they attended on Day 9 in Cycle 1 the hormone sample must be taken on Day 9 in Cycle 2, and so on).

If the subject unexpectedly cannot attend on Days 1-3 of their next menstrual cycle they can remain in the study and Cycle 2 will be scheduled for their next menstrual cycle. Clinic staff should keep in close

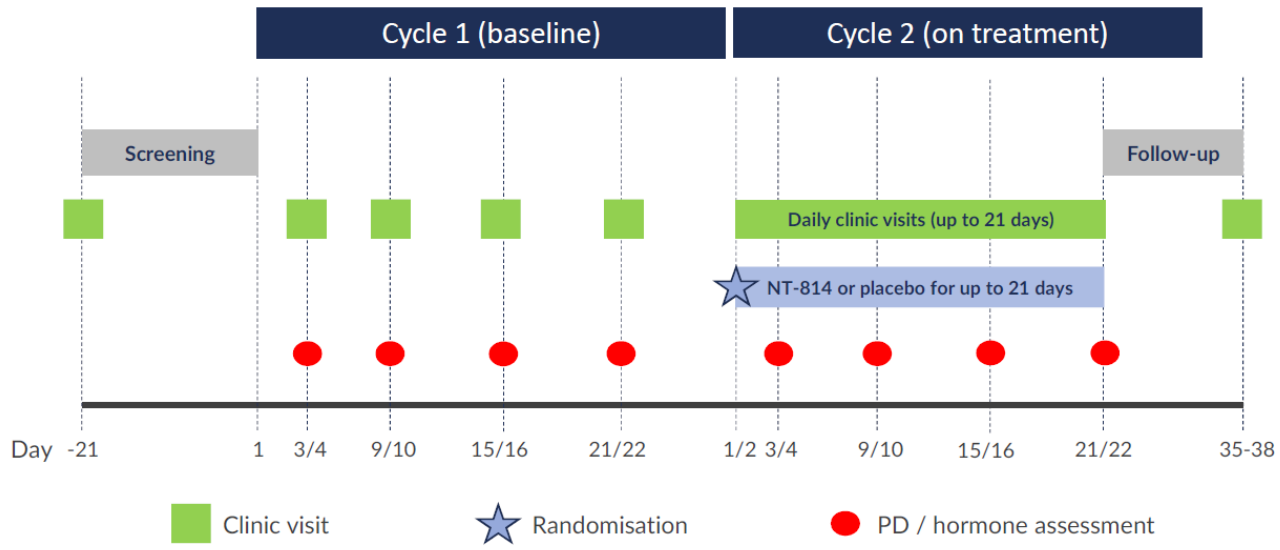
contact with the subject and instruct them to attend the clinic on Day 1 or 2 (or 3 in exceptional circumstances) of their subsequent menstrual cycle. Because of the delay between randomization and the previous safety laboratory assessments (performed Day 21/22 Cycle 1), these subjects will need to attend the clinic on Day 1 or 2 early enough to ensure that safety laboratory samples can be taken, and the results assessed prior to randomization and dosing.

Safety will be monitored throughout the study with routine safety assessments (AE recording; vital signs; 12-lead ECG; clinical laboratory tests). A physical examination will be conducted at screen and follow-up. Additional safety assessments will be done at any time as considered appropriate by the Investigator. Additional safety assessments not specified in the protocol may be performed as required by Quotient Sciences Standard Operating Procedures, but these will not be entered into the eCRF. Any abnormal assessments observed during non-protocol required safety assessments will be recorded as AEs if appropriate and the corresponding abnormal assessment entered as an unscheduled assessment in the eCRF.

Subjects will have a final outpatient follow-up visit two weeks following the final dose of study medication. At this visit the subject will be asked when their next menstrual cycle started (the cycle after the completion of dosing).

An overview of the study is shown in Figure 6-1.

Figure 6-1: Study Schematic



7 STUDY POPULATION

Potential subjects will be identified from the study unit's database of volunteers or via advertisement. Study-specific advertisements must be approved by the Institutional Review Board (IRB) before use. Potential subjects will be contacted by a dedicated recruitment officer who will invite them to participate in this study and schedule screening assessments.

The Investigator will maintain a confidential Screening Log of all potential study candidates, including each candidate's name or initials and the date and outcome of the screening process (e.g. enrolment in the study, reason for ineligibility). In addition, the Investigator will maintain an Enrolment Log of all subjects enrolled in the study, giving limited information about the subjects including screening number and assigned study number. The Screening Log and Enrolment Log together allow the Investigator to find out the identity of any subject when necessary.

Subjects will be considered enrolled in the study as soon as they have undergone their first assessment in Cycle 1.

7.1 Subject Numbers

Thirty-two (32) healthy pre-menopausal female subjects will be enrolled in Cohort 1. If Cohort 2 is required, a further 10 healthy pre-menopausal female subjects will be enrolled.

Subjects who do not complete the study may be replaced. A maximum of 10 additional subjects to replace subjects who withdraw may also be enrolled.

7.2 Selection Criteria

Individuals are eligible for the study if they meet all of the inclusion and none of the exclusion criteria. The criteria below will be assessed at a screening visit within 21 days before the expected start of Cycle 1. Continued subject eligibility will be verified at the clinic visit on Day 3 or 4 of Cycle 1 and again prior to the start of dosing in Cycle 2.

7.2.1 Inclusion Criteria

Study subjects must:

1 Healthy, female, aged 18 to 45 years inclusive (age at time of informed consent)

2 Regular (approximately) monthly menstrual periods

3 Be able and willing to understand and comply with the requirements of the study and give written informed consent

4 Have a body mass index (BMI) in the range 18.0 to 32.0 kg/m^2 and body weight not less than 40.0 kg

5 Be judged to be in good health, based on the results of medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory findings

6 Not be pregnant and not lactating, with no intention of pregnancy during study treatment

7 Agree to use two acceptable methods of birth-control, one of which is a barrier method with spermicide[1] (see Section 8.8.2) for the duration of participation in the study and 30 days after the last dose of study medication

7.2.2 Exclusion Criteria

Subjects must not:

1 Have been previously enrolled in this study or any other study with NT-814

2 Have clinically significant findings on physical examination at screening

3 Have any relevant medical history, in particular: liver or renal insufficiency, cholecystectomy, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances, any inflammatory illness or any other condition that the Investigator considers should exclude the subject

4 Have undergone bilateral oophorectomy and/or hysterectomy

5 Have positive serology for any of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)

6 Have any serum biochemistry and full blood count outside the normal reference ranges and considered by the Investigator to be of clinical significance, assessed at screening and on Cycle 1 Day 21/22. Hemoglobin must not be less than 11.0 g/dL at either screening or Day 21/22.

7 Have Stage 2 or higher hypertension (supine/semi-recumbent systolic blood pressure [SBP] >160 mmHg; diastolic blood pressure [DBP] >100 mmHg or Stage 1 hypertension (supine/semi-recumbent SBP 140–160 mmHg; DBP 90–100 mmHg associated with indication for treatment ie, evidence of end-organ damage, diabetes or a 10-year cardiovascular risk, estimated using a standard calculator, e.g. https://qrisk.org/three/, greater than 20%. Measurements will be based on the mean of duplicate values recorded at least 2 minutes apart and will be assessed at screening, on Cycle 1 Day 21 or 22 and pre-dose on Cycle 2 Day 1 or 2. Out of range measurements may be repeated once at each time point.

8 Have clinically relevant abnormal 12-lead ECG, including QT interval corrected for heart rate according to Fridericia (QTcF) >450 ms, QRS interval >120 ms, PR interval >220 ms, assessed at screening, on Cycle 1 Day 21 or 22 and pre-dose on Cycle 2 Day 1 or 2; if any value is out of range, 2 repeated assessments are permitted at that time point and the value will be based on the mean of the triplicate measure

9 Have a history of any grade of drug- or alcohol-use disorder according to Diagnostic and Statistical Manual of Mental Disorders 5 criteria[35] (or later edition if applicable) within 6 months before Screening or have a positive test result(s) for drugs of abuse (opiates including methadone, cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, and benzodiazepines) at screening, Cycle 1 Day 21 or 22, or Cycle 2 Day 1 or 2

10 Have a clinically significant acute illness within 7 days before first study drug administration

1 Acceptable methods of birth control are surgical sterilization of the subject's male partner, if he is the sole partner of that subject; surgical sterilization by bilateral tubal ligation, a non-hormonal intrauterine device (IUD) inserted at least one month before study drug administration and to remain in place for at least 30 days after the last dose of study drug; barrier methods such as male condom or cap, diaphragm or sponge with spermicide. An exclusively homosexual or abstinent lifestyle s also acceptable, provided it is maintained throughout the duration of the study and for 30 days afterwards.

11 Drink, on average, more than 6 cups of coffee or other caffeinated beverages daily (where each cup of coffee or beverage contains approximately 120 mg caffeine)

12 Smoke more than an average of 5 cigarettes (or equivalent) per day

13 Have used any non-permitted prior prescription, over-the-counter or herbal medication (see Section 8.8.1)

14 Have a history of clinically significant drug and/or food allergies, particularly known allergy to any of the excipients used in the study medications (see Section 8.1)

15 Have received an investigational drug (including vaccines) or used an investigational medical device within 3 calendar months before the first dose of study medication or be currently enrolled in an investigational study

16 Have had major surgery within 2 calendar months before first dose of study medication, or have surgery planned during the time the subject is expected to participate in the study

17 Have donated blood or experienced acute loss of a significant amount of blood within 3 calendar months before first dose of study medication

18 Have psychological and/or emotional problems that would render the informed consent invalid or limit the ability of the subject to comply with the study requirements

19 Have any condition for which, in the opinion of the Investigator, participation would not be in the best interest of the subject or that could prevent, limit, or confound the protocol-specified assessments.

7.3 Duration of Subject Participation

Subjects will be in the study for approximately 12 weeks, from screening through to the final Follow-up visit.

7.4 Early Subject Discontinuation or Withdrawal

Subjects may withdraw from the study at any time without stating a reason and without prejudice to further treatment. The Investigator may withdraw a subject from the study and discontinue study treatment and assessments at any time.

Early discontinuation of any subject who has given informed consent to participate will be recorded including the reason for discontinuation. The primary reason for a subject withdrawing prematurely will be selected from the following standard categories of early discontinuations:

- Failed to meet enrolment criteria (screen failure)
- Adverse event: clinical events occurred or laboratory results are reported that, in the medical judgment of the Investigator are grounds for discontinuation from participation, in the best interests of the subject
- Withdrawal of consent: the subject desired to withdraw from further participation in the study; the subject is not obliged to provide any reason for withdrawal of consent, but where a reason is given this will be recorded on the electronic case report form (eCRF)
- Protocol violation: the subject failed to adhere to the protocol requirements, e.g. the subject started taking a prohibited medication

- Lost to follow-up: the subject stopped coming for visits and study personnel were unable to contact the subject
- Other: the subject was withdrawn for a reason other than those listed above.

Any subject discontinuing study treatment, for example due to an AE considered related to study drug, may be asked to consent to continue in the study for relevant safety assessments and PK and PD sample collections. Priority must be given to safety assessments.

If a subject withdraws from the study, the Investigator should complete and report the observations as thoroughly as possible up to the date of withdrawal and the reason for withdrawal. The Investigator will ask all withdrawn subjects to consent to a follow-up examination, to check that they have come to no harm as a result of taking part in the study. Provided that subjects agree, they will undergo the standard medical examination and laboratory tests that they would have undergone had they completed it.

The Investigator will immediately (within 24 hours after discontinuation) notify the Sponsor. Subjects who withdraw from the study may be replaced at the discretion of the Sponsor if needed to achieve the objectives of the study.

8 STUDY MEDICATION AND ADMINISTRATION

8.1 Study Medication

The investigational medicinal product (IMP) is NT-814 in the free-base form, formulated as a 40-mg unit dose in a soft-gelatin capsule or matching placebo capsule. Inactive ingredients in both the active and placebo capsules are Capmul MCM EP, Labrasol ALF, Tween 80, Peceol and Vitamin E.

The physical, chemical, pharmaceutical formulation properties and characteristics of NT-814 are described in the IB[33].

8.2 Rationale for Selection of Doses in the Study

NT-814 has previously been administered to humans in a number of different dosage forms. As described in Section 4.4, the doses proposed in this study are currently being studied in women with hot-flashes associated with the menopause. The exposures associated with these doses in the soft gel capsule formulation have previously been shown to be associated with evidence of target engagement on the GnRH pathway.

8.3 Allocation to Treatment

The study will be conducted in a single-blind manner.

At screening, each subject will be assigned a unique screening number.

On Cycle 2 Day 1 or 2, subjects who continue to meet the eligibility criteria will be randomized to treatment groups as follows:

Cohort 1

NT-814 40 mg	8 subjects	Subject numbers 1001 to 1032
NT-814 80 mg	8 subjects	
NT-814 120 mg	8 subjects	
Placebo	8 subjects	

Cohort 2

NT-814 160 mg	8 subjects	Subject numbers 1033 to 1042
Placebo	2 subjects	

Cohort 1 will be enrolled first. Cohort 2 may be required dependent on review of the pharmacodynamic data from Cohort 1.

In the event that a subject is to be replaced, the replacement subject will be assigned the subject number of the subject she replaced to which 100 has been added and receive the same treatment as was planned for the original subject. Thus, Subject 1001 would be replaced by Subject 1101 and receive the treatment assigned to Subject 1001.

8.4 Study Treatment and Administration

All subjects will receive 4 capsules per day with placebo capsules being used to make up the count in subjects randomized to doses lower than 160 mg.

Dose	IMP Supply
Placebo:	4 x placebo capsules
40 mg:	1 x NT-814 capsule + 3 x placebo capsules
80 mg:	2 x NT-814 capsules + 2 x placebo capsules
120 mg:	3 x NT-814 capsules + 1 x placebo capsules
160 mg:	4 x NT-814 capsules

Subjects will take capsules at the assigned dose as a single oral dose on the mornings starting on Day 1 or 2 of Cycle 2 and continuing until the day prior to the final PD assessment on Day 21 or 22. Subjects will attend the clinic first thing in the morning for dosing and assessments, as per the schedule. The timing of each visit should be such that the dose of study medication is taken approximately 1-2 hours after having breakfast at home. Doses will be taken with 240 mL water.

Every effort should be made to administer study treatment on the planned dose and schedule. No dose modifications are permitted.

8.5 Packaging and Labelling

The investigational site will be provided with bulk drug supplies (NT-814 40 mg soft-gel capsules and placebo to match) in alu:alu foil blister strips, packaged and labelled according to local regulatory requirements. All doses are given in the study unit. Directions for preparing individual doses will be provided.

8.6 Handling and Storage

IMP must be dispensed and administered according to procedures described in the Study Manual. Only subjects enrolled in the study may receive IMP. Only authorized site staff may supply or administer IMP. All IMP must be stored in a secure area with access limited to the Investigator and authorized site staff. The bulk IMP must be kept in the original packaging and stored at ambient room temperature (15 – 25°C). Maintenance of a temperature log (manual or automated) is required whilst IMP is held at the study site.

8.7 Investigational Medicinal Product Accountability

In accordance with regulatory requirements, the Investigator is responsible for IMP accountability, reconciliation, and record maintenance. The Investigator or designated site staff (e.g., pharmacist) must maintain accountability records for IMP throughout the course of the study. The responsible person(s) will document the amount of IMP received and returned (on behalf of NeRRe) and the amount administered to subjects. The accountability unit for this study is a capsule. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused IMP will be provided.

The Investigator has overall responsibility for ensuring that the study treatment is received and managed at the study site in accordance with Good Clinical Practice (GCP). Limited responsibility may be delegated to a nominated study site representative; such delegation must be documented.

The Sponsor will be permitted upon request to audit supplies, storage and dispensing records and procedures.

8.8 Other Study Restrictions

Subjects must fast for 8 hours before clinical safety laboratory tests and strenuous exercise is prohibited for 3 days prior to any safety laboratory tests.

From 48 hours before the first dose until the follow-up visit, subjects must **not** consume products containing grapefruit or Seville oranges.

Throughout the dosing period subjects must be instructed to limit their caffeine intake to no more than 4 cups of coffee or equivalent beverages per day (equivalent to 120 mg caffeine per beverage).

Donation of blood to any institute other than the study unit is not allowed for the duration of the study.

Light alcohol consumption is permitted throughout the study – not more than 7 units per week.

Light smoking is permitted throughout the study – but not more than 5 cigarettes (or equivalent) per day.

8.8.1 Prior and Concomitant Medication

Eligible subjects are healthy volunteers. It is expected that in the period before the start of the study they will have taken only infrequent medication to treat intercurrent conditions.

Subjects will be excluded if they have taken any prescription or nonprescription drug, vitamin, dietary supplement and/or herbal supplement that is a strong inducer of cytochrome P450 (CYP) metabolizing enzymes within 1 month, or any prescription or nonprescription drug, vitamin, dietary supplement and/or herbal supplement within 1 week (or 5 half-lives, if longer) before the first dose of study medication, with the exception of acetaminophen (paracetamol) at doses up to 2100 mg/day.

Subjects will also be excluded if they have taken any medication which will alter endogenous hormone levels especially hormonal contraceptives (given by any route) for the periods prior to the screening visit, as follows:

- $\geq$1 week for vaginal hormonal products (rings, creams, gels and including dehydroepiandrosterone [DHEA] or analogues thereof)
- $\geq$4 weeks for transdermal estrogen alone or estrogen/progestin products
- $\geq$8 weeks for oral estrogen (including selective estrogen receptor modulators) and/or progestin therapy
- $\geq$8 weeks for intrauterine progestin therapy
- $\geq$3 months (after removal or end of 5-year duration) for progestin implants and $\geq$3 months for estrogen alone injectable drug therapy
- $\geq$6 months for estrogen pellet therapy or progestin injectable drug therapy

Subjects must not discontinue prescribed medication to comply with these restrictions without prior approval from the prescriber.

Permitted concomitant medication comprises:

- Acetaminophen (paracetamol), at doses up to 2100 mg/day

- Medication needed to treat AEs. In selecting appropriate medication, the Investigator must consider the risk of drug-drug interaction involving NT-814 either as substrate or as perpetrator. See Section 4.5.2 for further information or contact the Sponsor's Medical Monitor. If concomitant medication needed to treat AEs is likely to be associated with increased risk to the subject or reduce the likelihood of achieving the study objectives, the subject should discontinue dosing with study medication and/or be withdrawn from the study.

With these exceptions, no other concomitant medication is allowed during this study from 1 week before first administration of study medication until the follow-up visit.

If the administration of any concomitant therapy becomes necessary, it must be reported on the appropriate eCRF page. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.8.2 Contraception

All subjects must agree to use two acceptable methods of birth control for the duration of participation in the study and 30 days after the last dose, one of which must be a barrier method with spermicide.

Acceptable methods of birth control are:

- Surgical sterilization of the subject's male partner (vasectomy with documented azoospermia), if he is the sole partner of that subject;
- A non-hormonal intrauterine device (IUD) with failure rate of less than 1% per year inserted by qualified physician at least one month before study drug administration and to remain in place for at least 30 days after the last dose of study drug;
- Barrier methods such as male condom or cap, diaphragm or sponge with spermicide

Women who lead either an abstinent or an exclusively homosexual lifestyle are not required to use two methods of contraception but are required to commit to this lifestyle for the duration of the study and 30 days after the last dose.

Hormonal contraceptives are not acceptable by any route (systemic, implants, depot, intrauterine).

Serum pregnancy tests will be done on women of child-bearing potential at screening and on Day 21 or 22 of Cycle 1, and a urine pregnancy test performed on Day 1 or 2 of Cycle 2 (prior to the first dose of study medication). All tests must be negative for the subject to continue in the study.

A final serum pregnancy test will be done at the final follow up visit.

9 STUDY ASSESSMENTS AND PROCEDURES

Please see Table 9-1 for the complete schedule of assessments. Section 9.6 summarizes the order of procedures when more than one activity is scheduled for the same time point and permissible time windows.

Table 9-1 Schedule of Events

	Screening	Cycle 1					Cycle 2					Follow-up
Day	**-21[a]**	**1**	**3/4**	**9/10**	**15/16**	**21/22**	**1/2**	**3/4**	**9/10**	**15/16**	**21/22**	**35-38**
Clinic visit (out-patient)	X		X	X	X	X	X ---------- X[e]					
Informed consent	X[b]											
Menstrual flow starts		X					X[l]					
Record dates of start of menstruation		X ---------- X										
Medical History	X											
Physical examination	X											X
Vital signs [c]	X					X	X[f]	X[h]	X[h]	X[h]	X	X
Oral or aural body temperature	X						X[f]					X
12-lead ECG	X					X	X[f]	X[h]	X[h]	X[h]	X	X
Weight	X					X	X					X
Serology [d]	X											
Drugs of abuse screen	X					X	X[f]					
Hematology and Clinical Chemistry	X					X	X		X		X	X
Serum pregnancy test	X					X						X
Urine pregnancy test							X[f]					
Sample for PD hormone assessment			X	X	X	X		X[h,i]	X[h,i]	X[h,i]	X[i]	
Sample for PK								X[h,j]	X[h,j]	X[h,j]	X[j]	
Randomization						X						
NT-814/placebo once daily							X ---------- X[g]					
Adverse Event / con med reporting [k]	X ---------- X											

a Screening to be scheduled within 21 days of the anticipated start of the next menstrual cycle. This period can be extended if the menstrual period starts later than anticipated.
b Informed consent can be obtained prior to the screening visit. The screening period starts from the date of the screening procedures, not from the date of consent.
c Vital signs: systolic and diastolic blood pressure, pulse
d Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, human immunodeficiency virus
e Daily clinic visits in the morning, starting on Day 1 or 2 of Cycle 2 and ending on Day 21/22.
f Performed prior to the first dose
g Doses administered in the morning, in the clinic ~1-2 hours after breakfast; starting on Day 1 or 2 of Cycle 2; last dose will be day prior to clinic visit on Day 21/22. Doses to be administered at the same time each day (±1hr).
h Prior to administration of dose on the days shown
i PD sample days must be the same relative to Day 1 on both Cycles 1 and 2
j PK samples taken on same day/time as PD samples in Cycle 2
k AEs and concomitant medication to be reported from the start of screening
l Requires visual verification

9.1 Informed Consent and Screening

Subjects will be provided with the Participant Information Sheet and Informed Consent Form for their prior review. Written informed consent to participate in the study must be obtained for all subjects before any study-related procedures are performed; subjects must personally sign and date the approved ICF and, where applicable, privacy statement.

All subjects will be screened within 21 days of the expected start of Cycle 1. This period can be extended if the menstrual cycle starts later than anticipated.

9.2 Safety Assessments

9.2.1 Medical History and Concomitant Disease

History should include (but not be limited to) respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric and any other diseases, and all current and past medications taken during the 3 months before the Screening Visit. In addition, the Investigator will record in the eCRF information to document compliance with Inclusion Criterion 7 (use of acceptable contraception) as applicable.

The Investigator must record all clinically relevant information, regardless of the time since the date of diagnosis.

9.2.2 Physical Examination

A full physical examination will be conducted at the screening and follow-up/early termination visits (Table 9-1) by the Investigator or a medically-qualified designee. A full physical examination comprises review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose and throat
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological

Formal physical examination is not required at other times, but a directed physical examination should be undertaken if indicated by an emergent AE.

Any abnormalities identified at the screening visit should be documented on the medical history eCRF page. Any new clinically significant changes identified at later time-points should be documented as an AE.

If an improvement/resolution of a physical examination finding documented in the subject's medical history/screening visit occurs during the study, it should be recorded in the source document. If there is resolution of a physical examination finding previously noted as an AE, then the event resolution and stop date should be recorded on the AE eCRF page and documented in the subject's notes.

9.2.3 Vital Signs

Vital signs will be measured at the time points indicated in Table 9-1 and will include systolic and diastolic BP, pulse, temperature and weight.

BP and pulse should be measured using a standardized process:

- After the subject has been at rest supine for at least 5 minutes
- Not within 15 minutes after venipuncture or cannulation

- Using an automated BP device, with an appropriately sized cuff, with the bladder centered over the brachial artery
- Using the same arm throughout the study

All measurements are to be recorded on the eCRF.

All vital signs must be reviewed by the Investigator or a medically-qualified designee, who will comment on all abnormal results and determine whether they are clinically significant. These assessments will be recorded in the eCRF. Clinically significant findings must also be reported as AEs in the eCRF.

9.2.4 12-lead Electrocardiograms

12-lead ECGs will be recorded at the time points indicated in the Study Schedule in Table 9-1. A single recording will be obtained after the subject has been at rest supine for at least 5 minutes and not within 15 minutes after venipuncture. An electronic copy or original paper copy (not a photocopy) of each ECG will be saved for possible future manual evaluation.

Cardiac intervals will be measured automatically, confirmed by the Investigator or a medically-qualified designee, and recorded. ECG intervals outside the local reference ranges or ECG interpreted as other than normal sinus rhythm or sinus arrhythmia should be commented on for clinical significance. The overall ECG must be reviewed by the Investigator or a medically-qualified designee and assigned one of the following categories:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

All abnormalities, whether clinically significant or not, must be recorded in the eCRF. An abnormal, clinically significant, finding that is present at baseline must be recorded in the medical history. An emergent clinically significant ECG finding should be recorded as an AE.

9.2.5 Adverse Events

AEs will be recorded from the Screening Visit until the Follow-up/Early Termination Visit (30 days after the last dose of study medication for serious AEs). In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as “How are you feeling?”

All AEs will be recorded on the appropriate pages in the eCRF and in source documents. Appropriate follow-up will be required for any AEs ongoing at study exit.

Definitions and reporting procedures are described in Section 10.

9.2.6 Clinical Laboratory Safety Assessments

Blood and urine samples will be collected at the time points shown in Table 9-1 for clinical laboratory safety assessments listed in Table 9-2.

Table 9-2 Clinical Laboratory Safety Tests

Chemistry	
Alanine aminotransferase	Creatine kinase
Albumin	Creatinine
Alkaline phosphatase	Glucose
Aspartate aminotransferase	Gamma-glutamyltransferase
Bicarbonate	Magnesium
Bilirubin (total)	Phosphate (inorganic)
Blood urea nitrogen/urea	Potassium
Calcium	Sodium
Chloride	Total protein
Hematology	
Hemoglobin	Mean corpuscular hemoglobin concentration
Hematocrit	Mean corpuscular hemoglobin
Red blood cell count	White blood cell count with differential
Mean corpuscular volume	Platelets
Urinalysis	
Bilirubin	Nitrite
Blood	pH
Glucose	Protein
Ketones	Specific gravity
Leukocyte esterase	Urobilinogen
Microscopic examination (if urine protein, blood, nitrite, or leukocyte esterase values are out of range)	
Other	
Urine for drugs of abuse, including opiates (including methadone); cocaine; amphetamines; methamphetamines; cannabinoids; barbiturates; and benzodiazepines	
Serology: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis C (HCV) antibody, human immunodeficiency virus (HIV)	
Serum/ urine pregnancy test	

Samples will be collected and handled in accordance with the analytical laboratory's standard procedures. The analytical laboratory will perform blood safety tests and urinalysis using instruments interfaced to a validated general laboratory information management system.

All laboratory test reports must be reviewed, signed and dated by the Investigator or a medically-qualified designee, and filed with the subject's medical record. The Investigator will comment on all results outside the local reference range and determine whether they are clinically significant. Clinically significant findings must also be reported as AEs in the eCRF.

A positive result in any serology parameter will exclude the subject from participation in the study. Pregnancy tests must be negative for the subject to enter or continue in the study. Any pregnancy should be reported as detailed in Section 10.2.

9.3 Pharmacodynamic (Hormone) Assessments

Blood samples will be collected at the time points shown in Table 9-1 for assessment of serum LH, FSH, estradiol and progesterone.

Samples for assessment of estradiol and progesterone will be analyzed using an ultrasensitive liquid chromatography – mass spectrometry (LC-MS/MS) assay. LH and FSH will be analyzed by immunoassay.

Samples will be collected and handled in accordance with the analytical laboratory's standard procedures. The analytical laboratory will perform hormone tests using instruments interfaced to a validated general laboratory information management system.

9.4 Pharmacokinetics

9.4.1 Sample Collection and Handling

Blood samples will be collected at the time points shown in Table 9-1 for assay for plasma concentration of NT-814.

9.4.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of NT-814 at Aptuit Srl, Verona, Italy, using the current Sponsor-approved validated analytical methodology. Raw data will be stored in the Good Laboratory Practice archive of Aptuit.

Plasma concentration data will be transferred to Quotient, which will be responsible for generating the relevant tables and listings.

9.4.3 Pharmacokinetic Analysis

Formal pharmacokinetic analyses will not be performed.

9.5 Volume of Blood Sampling

Table 9-3 shows the estimated total blood volume requirements for the study.

Table 9-3 Estimated Blood Sample Volume Requirements

	Volume per sample mL	Number of samples	Total Volume mL
Serology	3.5	1	3.5
Hematology	3	3	9
Biochemistry	3.5	3	10.5
Sample for PD (hormones)	10	8	80
Samples for PK	4	4	16
TOTAL VOLUME			**119 mL**

The volume required for safety samples may vary accordingly to local laboratory requirements. However, the total volume is not expected to exceed 350 mL per subject.

9.6 Priority Order of Study Assessments; Permitted Windows

Note the following with regard to sequence of tests and acceptable time windows.

- Informed consent can be obtained before the actual screening visit, with the 21-day screening period starting from the date of the screening visit and not the date consent is obtained
- Predose procedures on Day 1 or 2 of Cycle 2 must be completed before the first dose
- Assessments on Cycle 2 Days 3 or 4, 9 or 10, and 15 or 16 should be performed prior to dosing
- As far as possible, each subject should be dosed at the same time of day during the dosing period in Cycle 2; however, a window of ±1hr is permitted
- The serum hormone sampling days relative to Day 1 of Cycle 2 will match the days samples were taken in Cycle 1 (relative to Day 1 of Cycle 1) within each subject (e.g. if the subject attended the clinic on Day 4 in Cycle 1, the hormone sample must be taken on Day 4 in Cycle 2; if they attended on Day 9 in Cycle 1 the hormone sample must be taken on Day 9 in Cycle 2, and so on).
- Collection of samples for hormone assessment should be performed at approximately the same time of day throughout Cycles 1 and 2; however, a window of ±1hr is permitted
- Measurement of vital signs and ECG recordings should be avoided within 15 minutes after venipuncture and, therefore, should normally be done before blood sampling.

The Investigator may repeat tests, conduct tests other than those specified, and schedule additional visits in the event of a technical failure and/or if extra observations or samples of blood or urine are needed to monitor subject safety. These will not be considered protocol deviations.

Any deviation outside these permitted windows must be noted in the subject's clinic chart and eCRF.

10 ADVERSE EVENTS AND PREGNANCY

10.1 Adverse Events

10.1.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR): all events considered untoward and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., a relationship cannot be ruled out.

Serious Adverse Event (SAE)
An adverse event that, at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalizations are defined as initial or prolonged admissions that include an overnight stay. Attendance at an Emergency Room that extends overnight but does not result in formal admission is not considered an overnight stay. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event is also not an SAE.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered to be an important medical event

  Based upon medical and scientific judgment, important medical events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the subject and may require intervention to prevent one of the other outcomes listed in the definition above may be considered an SAE.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with applicable reference safety information in the IB.

Reports that add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An SAE that is suspected to be related to the administered medicinal product, and the nature or severity of which is not consistent with applicable reference safety information.

10.1.2 Assessment of Severity

The medically-qualified Investigator should classify the severity (intensity) of each AE as:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Sign or symptom causes discomfort, but does not interfere with normal activities
Severe	Sign or symptom of sufficient intensity to interfere with normal activities

10.1.3 Assessment of Causality

The medically-qualified Investigator must determine the relationship to study treatment for each AE as **Unrelated** or **Related**.

In assessing the causality, the Investigator will take into consideration the known safety profile of NT-814 from prior clinical experience, the findings from non-clinical safety assessments, the temporal relationship with dosing, any effect of de-challenge or re-challenge, the subject's past medical history, the contribution from study procedures or restrictions, and the use, if any, of concomitant medications.

10.1.4 Serious Adverse Event Reporting

Once the Investigator determines that an event meets the protocol definition of an SAE, he/she must report the SAE to the Pharmacovigilance Service Provider, Emas Pharma, immediately (within 24 hours). Any follow-up information on a previously reported SAE will also be reported to Emas within 24 hours.

If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying Emas of the event and completing the appropriate data collection form. The Investigator will always provide a preliminary assessment of causality at the time of the initial report.

Emas Pharma contact details for SAE submission can be found at on the front page of this protocol.

The primary mechanism for reporting SAEs to Emas Pharma will be a paper collection form.

Fax transmission or 'scan & email' of the SAE form is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of either email or fax equipment, notification by telephone is acceptable, with a copy of the SAE data collection form sent by overnight mail. Initial notification via the telephone does not replace the need for the Investigator to complete and sign the SAE data collection form within the designated reporting periods

The Investigator must notify his or her IRB of the SAE, as required by local regulatory authorities and in accordance with IRB policy. NeRRe will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

All SUSARs that occur with the IMP within or outside the concerned clinical trial will be reported in compliance with the applicable regulatory authorities and IRBs. Fatal or life-threatening SUSARs must be reported within 7 calendar days and other SUSARs within 15 calendar days.

10.2 Pregnancy

Female subjects will be instructed that they should report to the Investigator if, despite the measures in place to prevent pregnancy, they become pregnant during the study or within 30 days after their last dose of IMP, including any pregnancy occurring during the study but confirmed after completion of the study.

Any female subject reporting a pregnancy during the study will be withdrawn from the study immediately; no further IMP may be administered.

In the event that a subject becomes pregnant during or within 30 days after the end of the study, the Investigator will collect and record information on that pregnancy on the appropriate form and submit it to Emas within 24 hours of learning of a subject's pregnancy through the same process as reporting an SAE. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Emas. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Pregnancy itself is not considered an AE. However, any pregnancy complication, spontaneous or elective abortion for medical reasons, still birth, neonatal death, or congenital anomaly will be recorded as an AE or SAE as applicable.

11 STATISTICAL CONSIDERATIONS

Statistical analysis and reporting will be performed by Quotient.

11.1 Sample Size

In total, up to 42 subjects will be enrolled into the study, 8 per active dose level and 10 on placebo. No formal sample size assessment has been conducted but this sample size is considered sufficient for the objectives of the study to be achieved.

11.2 Analysis Sets

A subject is defined as a volunteer who was allocated a unique screening number. All subjects will be classified as one of the following:

- A screening failure is defined as a subject who signed the informed consent but did not satisfy the relevant inclusion/exclusion criteria prior to Cycle 1.
- An enrolled subject is defined as either:
  - a subject who signed the informed consent, was considered to have satisfied all the relevant inclusion/exclusion criteria prior to Cycle 1, started Cycle 1 (i.e. completed the PD sample procedures on Day 1/2, Cycle 1), was not randomized and did not receive any Investigational Medicinal Product (IMP);
  - or a subject who signed the informed consent, was considered to have met the relevant inclusion prior to and during Cycle 1, was randomized and received at least one dose of IMP.

The following data sets will be used for the statistical analysis.

Enrolled Set: All enrolled subjects as defined above.

Safety Set: All enrolled subjects who received at least one dose of IMP. Subjects will be analyzed according to treatment (dose level) received.

Pharmacodynamic (PD) Set: all subjects in the Safety Set for whom there is adequate Clcyle 2 and Cycle 2 PD data to derive the primary endpoints.

Analysis sets will be identified prior to analysis of the study data.

11.3 Data Analysis and Reporting

Full details of the proposed statistical and pharmacodynamic analyses will be documented in the Reporting and Analysis Plan (RAP), which will be written following finalization of the protocol and finalized before locking the database.

Where applicable, values will be converted from local to Système International (SI) units for reporting; both original and converted values will be listed.

PD and safety data will be presented by means of descriptive statistics and figures, as appropriate, by treatment arm and time point. All data will be listed.

Summary statistics will be based primarily on non-missing values. Full details on the handling of missing values will be defined in the RAP.

11.3.1 Baseline assessment

Descriptive statistics will be performed on relevant screening and baseline data (i.e. data collected prior to the treatment administration) and on demographic characteristics for each treatment group.

In general, baseline for safety assessments will be the last value recorded before the first dose of IMP. Baseline for PD assessments will be the time-matched value from Cycle 1.

11.3.2 Safety analysis methodology

The safety and tolerability profile will be assessed versus baseline conditions, and descriptive statistics for change from baseline will be produced, where applicable.

A treatment-emergent analysis will be done for AEs. AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. Tabulations by severity and drug-relatedness will also be made.

Safety data will be summarized by dose of NT-814 including placebo.

11.3.3 Pharmacodynamic analysis methodology

The pharmacodynamic data (i.e. LH, FSH, estradiol and progesterone) in Cycle 2 will be assessed versus baseline (Cycle 1), and descriptive statistics for change from baseline will be produced, where applicable.

The changes from baseline will be analyzed using a fixed effects model with treatment as a fixed effect and the corresponding baseline value as a covariate. The adjusted arithmetic means from the model for the changes from baseline including 95% confidence interval (CI) will be presented for each treatment. In addition, the following comparisons will be performed and the difference in the adjusted arithmetic means and 90% CI will be presented:

- each dose level of NT-814 vs placebo

This analysis will be performed for each day separately (i.e. Days 3/4, 9/10, 15/16 and 21/22). A repeated measures analysis may be used if considered appropriate.

For the exploratory analysis of the change in menstrual cycle length, the length of Cycle 2 will be assessed versus baseline (length of Cycle 1), and descriptive statistics for change from baseline will be produced, where applicable.

11.3.4 Pharmacokinetic-Pharmacodynamic Analysis Methodology

Plasma concentrations of NT-814 will be summarized descriptively; possible exposure-response relationships may be explored.

12 END OF THE STUDY

The end of the study is defined as the date of last contact (visit, telephone call, email, etc) with any study subject.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Institutional Review Board (IRB) and Relevant Authorities

The final study protocol and the subject information and consent form, together with any materials used to aid subject recruitment, will be approved by an appropriately constituted independent IRB. Approval must be received in writing before initiation of the study.

13.2 Ethical Conduct of the Study

The study will be performed in accordance with the local regulations, the requirements of GCP, as described by the International Council for Harmonization (ICH), and the ethical principles that have their origins in the Declaration of Helsinki.

13.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the Principal Investigator or one of his/her associates will explain orally and in writing the nature, duration, purpose of the study, and the action of the study drug in such a manner that the subject is aware of the potential risks, inconveniences, and adverse effects that may occur. They will be informed that their medical records may be reviewed by appropriately qualified monitors of the Sponsor or Sponsor Representative, and by auditors or regulatory authorities to ensure the accuracy of the details recorded as part of the study. They will be informed that they may withdraw from the study at any time without prejudice to further treatment. They will receive all information that is required by local regulations and ICH guidelines.

14 STUDY AND DATA MANAGEMENT

14.1 Protocol Amendments

Once approved by the applicable Regulatory Authorities and IRB, the protocol must not be amended without approval by NeRRe. Unless an amendment is required to be implemented urgently in the interests of safety, any amendments to the protocol must be authorized by the applicable IRB prior to implementation. The Sponsor will determine whether regulatory authority approval or notification is required prior to implementing an amendment.

14.2 Monitoring

In accordance with the requirements of GCP, a clinical study monitor will review the source data and study conduct throughout the trial. All data recorded in the eCRF must be supported by source documentation in the subject records held at the investigative site. A list of what is to be classed as source documentation will be documented in the Study Monitoring Manual.

On behalf NeRRe, the clinical study monitor will verify that:

- the data are authentic, accurate and complete;
- the safety and right of the subjects are being protected;
- the investigational product is fully accounted for;
- all SAEs have been identified and reported; and
- the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements.

The Investigator agrees to allow the monitor direct access to all relevant documents.

NeRRe will appoint a medical monitor to oversee the medical aspects of the study. The medical monitor will be available for the Investigator to consult in the event of any questions or concerns about the safe conduct of the study.

14.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, NeRRe may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/ inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/ inspector direct access to all relevant documents and to allocate his/ her time and the time of his/ her staff to the auditor/ inspector to discuss findings and any relevant issues.

14.4 Data Management

An eCRF will be used to capture subject data. Access to enter data in the eCRF will be limited to delegated and trained study site staff.

Data management will be performed by Quotient Sciences.

Within the eCRF, subjects will only be identified by their unique subject number.

All study data recorded in the eSource that are relevant for reporting the study will be transcribed into a validated study database which has an audit trail to log all subsequent changes to the data. The database is compliant with 21 Code of Federal Regulation Part 11 guidelines. All queries will be resolved within the study database.

Adverse events and medications will be coded using MedDRA (v22.0 or a more recent version) and the World Health Organization (WHO) Drug Dictionary Global Drug Reference List [B3/C3] (2019 or a more recent version), respectively. An independent coding review will also be performed within the Data Sciences department.

Clinical chemistry and hematology data (and other safety laboratory data) will be collected by a central laboratory and stored electronically in their laboratory information system. The data will be transferred electronically to Quotient Sciences and all demographic details and sample dates will be cross-referenced with the corresponding data on the study database. All queries will be resolved with the assistance of laboratory staff, or if necessary, clinical staff.

The database will be closed after all queries have been resolved. The database will be locked when all criteria listed in the Data Management Plan are met.

Further details are addressed in the Data Management Plan.

14.5 Confidentiality

Study data will be handled with utmost discretion within the context of physician's confidentiality. On the eCRFs and other study specific documents, subjects will be identified by a unique subject number; names and initials will not be captured. Names of participating subjects and data generated as a result of this study will not be passed on to unauthorized persons.

The Investigator must assure that the subject data are properly anonymized throughout the study. On all study documentation which is to leave the site (i.e., to be transmitted to NeRRe, contract research organization [CRO] or third parties), subjects will only be identified by their unique identification code and will not be referred to by name.

NeRRe may transfer some data collected during the study to a different company or regulatory authority outside of the US for the purpose of processing, review, analysis or storage. Whenever the subject's personal data is transferred, it will be kept confidential and secure, and will be used only for the purpose for which it was collected.

Samples for safety analysis collected during the study will be analyzed at the local or central laboratory according to its procedures. All safety samples will be destroyed after the assays have been completed.

NT-814 PK samples will be shipped to Aptuit Srl, Italy for analysis. Analysis of the PK samples will be conducted after completion of the clinical phase of the study with the results included in the final study report. Following completion of the analysis, all samples will be destroyed. Analysis of samples for metabolite identification will be performed separately and will be reported separately. Once analysis is complete samples will be destroyed.

14.6 Retention of Study Data

Following closure of the study, the Investigator must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (e.g., audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the originals, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an

acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

NeRRe will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or NeRRe, or delegated CRO's standard operating procedures (SOP); otherwise, the retention period will default to 15 years.

The Investigator must notify NeRRe of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the Investigator leaves the site. The Investigator may not dispose of any records without prior approval from NeRRe.

14.7 Communication and Publication of Results

The Investigator will be provided appropriate access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at NeRRe or another mutually agreeable location.

The original eCRFs and all data generated during the study under this protocol will become the property of the Sponsor.

Upon completion of the clinical study report, NeRRe will ensure public disclosure of the clinical trial research results according to the NeRRe's SOP and provide the Investigator with the full summary of the study results.

Any proposed publication or presentation arising from this study (including a manuscript, abstract or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review at least 60 days prior to submission. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. The Sponsor may delay such submission by a maximum of six months if it reasonably believes that publication of results may compromise its intellectual property rights or else insist that such information or data is removed from the proposed publication. Publication of the results will not include confidential information without the permission of the Sponsor.

14.8 Indemnification

In the event of study-related damage or injuries, the clinical trial insurance of the Sponsor provides compensation for claims that arise in accordance with the regulatory requirements of the countries involved, except for claims that arise from willful misconduct or gross negligence. A copy of the country-specific insurance certificates will be held in the Trial Master File and in the Investigator Site File.

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16 SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Sponsor Approval

I have reviewed and approved the protocol and confirm that the protocol follows GCP.

Signature: _____ Date: _____

Stephen Pawsey MBBS FRCA FFPM
Chief Medical Officer, NeRRe Therapeutics Ltd.

Principal Investigator Agreement

I agree to conduct the study according to the terms and conditions of this protocol, current Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signature: _____ Date: _____

Maricer Escalon, MD MA MBA
Principal Investigator