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Protocol

OLP-1002 – A First-in-human, Double-blind, Placebo-controlled, Single and Multiple Subcutaneous Dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Male and Female Subjects

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SPONSOR APPROVAL

I have read the protocol and approve it:

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[redacted]

September 30, 2019

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

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STUDY IDENTIFICATION

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SYNOPSIS

Title of study: OLP-1002 – A first-in-human, double-blind, placebo-controlled, single and multiple subcutaneous dose, safety, tolerability, pharmacokinetic, and pharmacodynamic study in healthy male and female subjects
Objectives: The primary objective of the study is to assess the safety and tolerability of single and multiple subcutaneous doses of OLP-1002 in healthy subjects. The exploratory objectives of the study are to evaluate the pharmacodynamic effect of OLP-1002 following single subcutaneous doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of a single subcutaneous doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.
Study design: This will be a double-blind, randomized, placebo-controlled, single and multiple subcutaneous dose study conducted in 2 parts, including healthy male and female subjects.
Number of subjects: Part A: 68 subjects will be studied in 11 groups (5 groups of 4 and 6 groups of 8). Part B: 32 subjects will be studied in 4 groups (Groups B1 to B4).
Diagnosis and main criteria for inclusion: Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 28.0 kg/m^2 (inclusive).
Investigational products, dose, and mode of administration: Test product: OLP-1002 Proposed dose levels for Part A: 30 ng, 120 ng, 400 ng, 1.2 µg, 3 µg, 6 µg, 12 µg, 20 µg, 40 µg, 80 µg, and 160 µg. Proposed dose levels for Part B: the doses for Part B will be decided in consultation with the Sponsor and on the basis of data from Part A of the study. The highest daily dose in Part B will be up to 50% of the highest dose in Part A. Administration route: subcutaneous
Reference product and mode of administration: Reference product: placebo Administration route: subcutaneous
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to Follow-up): approximately 8 weeks for Part A and approximately 12 weeks for Part B.

Endpoints:

Pharmacodynamics:

In Part A, the analgesic effect of OLP-1002 will be investigated in 6 groups consisting of 8 subjects (6 active: 2 placebo) using experimental capsaicin-evoked pain methods. Measurement of capsaicin-evoked pain will be performed at pre-screening, baseline and on Day 2, and secondary hyperalgesia at 5 and 30 minutes post-capsaicin injection. Continuous electrocardiogram (ECG) recording will be conducted to investigate the effect of OLP-1002 on cardiac function.

Safety:

Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, heat pain threshold and tolerance, and physical examinations.

Pharmacokinetics:

In Part A, the following PK parameters will be determined where possible: area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$), maximum observed plasma concentration (C_{max}), time of the maximum observed plasma concentration (t_{max}), and apparent plasma terminal elimination half-life ($t_{1/2}$). PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

In Part B, the following PK parameters will be determined where possible: AUC over a dosing interval ($AUC_{0-\tau}$), $AUC_{0-\infty}$, $C_{max,}$ minimum observed plasma concentration (C_{min}), t_{max}, $t_{1/2}$, observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$), observed accumulation ratio based on C_{max} (RAC_{max}), and Temporal change parameter (TCP). PK samples from all groups in Part B will be analyzed.

Statistical methods:

Pharmacodynamics:

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of pharmacodynamic data is planned.

Safety:

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

Pharmacokinetics:

Individual plasma concentrations and PK parameters of OLP-1002 will be listed and summarized using descriptive statistics. Individual and mean OLP-1002 concentration-time profiles will be presented graphically.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours postdose
BMI	body mass index
C_{max}	maximum observed plasma concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSA	clinical study agreement
DN	Dose normalized
DRG	dorsal root ganglion
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
E_{max}	maximum pain intensity
FCA	Freund's Complete Adjuvant
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SC	subcutaneous(ly)
SNL	spinal nerve ligation
$t_{1/2}$	elimination half-life
tE_{max}	time of maximum pain intensity
T_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
VAS	Visual Analogic Scale
VGSC	voltage-gated sodium channel

1. INTRODUCTION

1.1. Overview

OLP-1002 is a novel peptide nucleic acid (PNA) derivative which acts as a specific voltage-gated sodium channel (VGSC) protein ($Na_v1.7$) inhibitor, and is being developed by OliPass for the treatment of pain.

The $Na_v1.7$ protein is a subtype of VGSCs. $Na_v1.7$ is particularly important in nociception and pain signaling, with congenital loss-of-function mutations in $Na_v1.7$ resulting in the inability to experience pain. Selective $Na_v1.7$ inhibitors are believed to have the potential to treat severe pain safely[1]. The active sites of VGSC subtypes are virtually indistinguishable by their 3-dimensional structure and thus the discovery of selective $Na_v1.7$ small molecule inhibitors has been extremely challenging. Since inhibition of $Na_v1.5$ subtype elicits long QT cardiotoxicity, inhibition of $Na_v1.5$ subtype should be avoided at therapeutic doses.

To date, there are several $Na_v1.7$ inhibitors claimed to be selective that have been evaluated in human subjects:

- Vixotrigine (formerly known as raxatrigine) inhibits $Na_v1.7$ as well as other VGSC subtypes. Vixotrigine is in phase III clinical development for trigeminal neuralgia. Due to the limited $Na_v1.7$ selectivity over $Na_v1.5$, vixotrigine was evaluated primarily in patients with a low heart risk.
- Funapide is a $Na_v1.7$ inhibitor with limited $Na_v1.7$ selectivity, and was in phase IIb clinical trials as of July 2014. Although funapide showed analgesic activity in a small number of erythromelalgia patients, dose-limiting adverse events (AEs), including dizziness and somnolence, were observed[2]. The central nervous system (CNS) AEs were due to its poor $Na_v1.7$ selectivity.
- PF-05089771 is a $Na_v1.7$ selective inhibitor with a claimed $Na_v1.7$ selectivity of > 2000-fold versus other subtypes of sodium channel and was evaluated in patients of erythromelalgia or dental pain. It is thought low drug concentrations achieved in the target tissue could be a possible explanation for its poor analgesic activity in human patients[3].

OLP-1002 is fully complementary to a 14-mer RNA sequence spanning the junction of intron 4 and exon 5 in the human SCN9A pre-mRNA which codes for the $Na_v1.7$ channel. OLP-1002 yields SCN9A mRNA splice variant(s) encoding variant $Na_v1.7$ protein(s) lacking the sodium channel activity (ie, a non-functional channel), thereby inhibiting $Na_v1.7$ channel function.

1.2. Summary of Nonclinical Pharmacology

1.2.1. In Vitro Pharmacology Studies

Overall, results from the in vitro pharmacology studies showed OLP-1002 elicits responses consistent with its designed function[4]. It inhibits SCN9A mRNA expression and yields the

$Na_v1.7$ variant protein or proteins lacking sodium channel activity. Its effects are highly selective, which may provide for an improved margin of safety compared to other $Na_v1.7$ inhibitors.

OLP-1002 at 1 to 100 zM in PC3 prostate carcinoma cells induced exon skipping and yielded SCN9A mRNA splice variant(s) encoding a $Na_v1.7$ variant protein or proteins lacking sodium channel activity.

In rat dorsal root ganglion (DRG) neuronal cells, OLP-1002 at 1000 zM inhibited $Na_v1.7$ protein expression by > 50%, while OLP-1002R at 100 and 1000 zM inhibited $Na_v1.7$ expression almost completely. As OLP-1002R is fully complementary to rat SCN9A pre-mRNA, OLP-1002R would be predicted to be more potent than OLP-1002 in this cell type.

SCN9A mRNA expression level was evaluated by quantitative polymerase chain reaction (qPCR). OLP-1002 inhibited the expression of the SCN9A mRNA in PC3 cells with sub-attomolar potency.

In SH-SY5Y human neuroblastoma cells stimulated with tumor necrosis factor (TNF)-1α to upregulate the expression of SCN9A mRNA, OLP-1002 decreased expression by 46% to 49% at 1 fM to 10 pM. In rat DRG neuronal cells, OLP-1002 at 1 fM significantly decreased SCN9A mRNA expression by 54%.

In rat DRG neuronal cells, OLP-1002 markedly and significantly inhibited the sodium current by 77% at 0.1 aM and 73% at 1 aM, while for OLP-1002R, the inhibition was 66% at 0.1 aM and 70% at 1 aM. Given that rat DRG neuronal cells express various subtypes of sodium channel, the observed inhibitions of 66% to 77% correspond to the complete knockout of the $Na_v1.7$ sodium channel subtype with OLP-1002 or OLP-1002R.

The $Na_v1.7$ selectivity over $Na_v1.5$ was evaluated in H9C2 rat cardiomyocytes which are known to abundantly express the rat $Na_v1.5$ sodium channel subtype. Following incubation with OLP-1002 or OLP-1002R at 1 aM or 1 pM, there were no notable decreases in the sodium current. Considering that OLP-1002 and OLP-1002R inhibit the expression of $Na_v1.7$ protein at 1 aM or lower in rat DRG neuronal cells, the $Na_v1.7$ selectivity of OLP-1002 and OLP-1002R over $Na_v1.5$ is estimated to be in excess of one million-fold. Such a large $Na_v1.7$ selectivity over $Na_v1.5$ has not been realized with small molecule $Na_v1.7$ inhibitors, suggesting that OLP-1002 potentially offers pain management with much greater cardiovascular safety.

1.2.2. In Vivo Pharmacology Studies

Spinal nerve ligation (SNL) has been widely applied as a rat model for neuropathic pain. OLP-1002 and OLP-1002R were found to be very potent, but highly variable in potency, in reversing neuropathic allodynia in this model. Analyses of the therapeutic potency strongly suggested that a marked proportion of subcutaneously (SC) administered OLP-1002 or OLP-1002R may have been topically delivered directly to the spinal nerves exposed in the dorsal cavity created during the SNL modelling. In addition, the variability of the therapeutic potency may be due to a variable degree of healing of the SNL surgery wound. If an animal

recovers slowly, the animal tends to be left with a dorsal cavity. Therefore, estimations of potency in these studies with this model should be treated with caution.

In one study using the SNL model, allodynia in rats was slowly and gradually reversed by OLP-1002 SC administered at nominal doses of 1, 3, and 6 pmol/kg once every 2 days (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). As the onset time for pain reduction was 4 days, the doses used were not sufficient for fast onset of activity. In this study, the animals should have reasonably recovered from the dorsal wound, and therefore less susceptible to topical delivery directly to the exposed spinal nerves. However, in another study in this model, when OLP-1002 was intraperitoneally (IP) administered once every 3 days to avoid the likelihood of local delivery to the spinal nerves, OLP-1002 surprisingly reversed the allodynia at 5 fmol/kg, and was superior or comparable to pregabalin 30 mg/kg, a gold standard for neuropathic pain studies. The high potency shown at 5 fmol/kg IP strongly suggests the possibility that OLP-1002 is efficiently absorbed by the enteric nervous system, travels to the spinal cord, and then redistributes to the spinal nerves of the SNL ligation. This opens the possibility of efficient oral delivery of OLP-1002 to the spinal cord.

When evaluated for their ability to reverse the inflammatory pain in rats inflicted with Freund's Complete Adjuvant (FCA)-induced severe paw inflammation, OLP-1002 at 300 pmol/kg and OLP-1002R at 100 pmol/kg significantly reversed the thermal hyperalgesia, and both were more effective than pregabalin 30 mg/kg. Two further studies investigating OLP-1002R at concentrations up to 10,000 pmol/kg using the FCA model showed a reversal of inflammatory allodynia in rats. Both studies demonstrated that maintenance of a steady state of efficacy over time was dose dependent, with the dose of 100 pmol/kg being sufficient over 1 day/30 hours postdose, and the higher doses of 1000 pmol/kg and 10,000 pmol/kg being the most suitable up to 3 days/96 hours postdose. Assuming that thermal withdrawal latency time of the normal control group was equivalent to 100% allodynia inhibition and that of the negative control group was equivalent to 100% allodynia induction, allodynia inhibition efficacy by OLP-1002R was estimated to be 20.65% ~ 45.48% and 34.21% ~ 58.72 % in the 2 studies. During both studies, no abnormalities or clinical finding were observed.

Paw burn injury induces hyperalgesia in rats and is known to upregulate $Na_v1.7$ expression in the L5 and L6 DRGs of the affected side. Burn injury induces a far weaker degree of paw inflammation than FCA-induced paw inflammation. OLP-1002 SC administered inhibited the thermal hyperalgesia in paw burn injury in a dose-dependent manner. At 25 fmol/kg, OLP-1002 did not inhibit thermal hyperalgesia. Although OLP-1002 at 625 fmol/kg significantly inhibited the thermal hyperalgesia, the efficacy was moderate and weaker than pregabalin 30 mg/kg. This suggests that SC dosing does not offer the local topical delivery to spinal nerves in this model as seen in rats without a dorsal cavity wound. In this study, the $Na_v1.7$ expression in the DRG of the burn injury side significantly decreased by 58% with 625 fmol/kg OLP-1002, validating the target engagement for analgesic activity.

An intraplantar injection of formalin induces severe acute pain. The contributors to acute pain are known to be complex and require further elucidation. However, acute peripheral inflammation is known to contribute much to Phase II Pain (pain from 10 to 40 min after the formalin injection). In this model, OLP-1002 significantly inhibited Phase II Pain at

comparable or saturated efficacy when SC administered at 10 to 100 pmol/kg (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). Thus peripheral acute inflammatory pain could be treated with 10 pmol/kg or less.

1.2.3. Ex Vivo Pharmacology Studies

One day post-SC injection, OLP-1002 and OLP-1002R at 100 pmol/kg significantly inhibited the expression of $Na_v1.7$ protein by 39% and 57%, respectively, in the spinal cord of rats subjected to SNL.

In other rats subjected to SNL, OLP-1002R slowly and gradually reversed the allodynia in a dose-dependent manner. OLP-1002R at 30 fmol/kg (the highest dose administered) had the greatest effect, but the dose was not high enough to elicit full therapeutic efficacy. OLP-1002R inhibited expression of $Na_v1.7$ protein in these animals, most notably at 1 fmol/kg, and decreased SCN9A mRNA expression by approximately 40% at 1 to 30 fmol/kg. The observed inhibitions were largely consistent with the in vivo therapeutic activity findings.

Taking all the in vivo and ex vivo findings together, OLP-1002R was concluded to inhibit neuropathic allodynia by inhibiting the expression of the SCN9A mRNA and the $Na_v1.7$ protein.

1.3. Summary of Safety Pharmacology

In vitro, OLP-1002 did not inhibit the human ether-à-go-go-related gene (hERG) channel current expressed in human embryonic kidney (HEK) cells at the highest concentration tested 2 μM (the limit of the validated analytical method for OLP-1002).

In the in vivo safety pharmacology studies, OLP-1002 SC administered at dose levels up to 100 nmol/kg had no effect on body temperature, neurological function, or respiratory function in rats, and had no significant toxic effect on cardiovascular function in cynomolgus monkeys.

1.4. Summary of Toxicology

In rats, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included pigment accumulation in the kidney of males administered 100 nmol/kg/dose and females administered ≥ 10 nmol/kg/dose, foreign material and vacuolated macrophage infiltrates in males and/or females administered ≥ 1 nmol/kg/dose, and an increased incidence and/or severity of mononuclear cell infiltrates at the injection sites in males and/or females administered ≥ 10 nmol/kg/dose. These findings persisted through the recovery phase in animals administered 100 nmol/kg/dose. However, the effects were considered non-adverse due to their mild severity and lack of impact on animal health and wellbeing. The no-observed-adverse-effect level (NOAEL) was 100 nmol/kg/dose. This dose level corresponded to maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from 0 to 24 hours postdose (AUC_{0-24}) values of 27.6 ng/mL and 174 ng.h/mL, respectively, in males and 24.9 ng/mL and 128 ng.h/mL, respectively, in females on Day 88 of the dosing phase.

In cynomolgus monkeys, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included mononuclear cell infiltrates at the SC injection sites of animals administered ≥ 10 nmol/kg/dose. This finding was not resolved with the completion of the recovery phase. However, the effects of 100 nmol/kg/dose were considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing. The NOAEL was 100 nmol/kg/dose (equivalent to 462.29 µg/kg/dose), which corresponded to C_{max} and AUC from 0 to 72 hours postdose (AUC_{0-72}) values of 121 ng/mL and 2840 ng.h/mL in males, respectively, and 216 ng/mL and 4840 ng.h/mL in females, respectively, on Day 88 of the dosing phase.

The genotoxic and mutagenic potential of OLP-1002 was evaluated with standard Good Laboratory Practice (GLP) via in vitro bacterial mutagenicity and chromosomal aberration studies, and was found to be negative.

1.5. Summary of Nonclinical Pharmacokinetics

In rats, following a single SC dose of ^{14}C-OLP-1002, the time of maximum observed concentration (T_{max}) was 0.5 to 1 hour for both radioactivity and parent compound. Plasma concentrations of total radioactivity were quantifiable through the last sampling time of 72 hours postdose, but was variable for the parent compound. The elimination half-life ($t_{1/2}$) of total radioactivity from plasma was 23 hours. Total radioactivity distributed into tissues, including those of the CNS protected by the blood-brain barrier. ^{14}C-OLP-1002-derived total radioactivity was not rapidly excreted from rats, with minimal amounts present in urine and feces. The bulk of the total radioactivity remained in carcasses, primarily in kidneys (cortex and medulla) and liver. Parent ^{14}C-OLP-1002 was present in plasma and tissues, but concentrations declined over time and were substantially lower than total radioactivity concentrations at the later sampling times.

After a single SC administration of ^{14}C-OLP-1002 to rats, the highest concentrations of total radioactivity were retained predominantly in the liver (10.4% to 13.3% of the dose), kidney cortex (3.47% to 4.96%), and kidney medulla (1.10% to 1.59% of the dose) through 168 hours postdose. For all other tissues, the total amounts of total radioactivity were substantially less, ranging from 0.0000203% in the 5th DRG to 0.327% in the spleen. Radioactivity was excreted slowly via both the renal and fecal routes of elimination. Total average recoveries of radioactivity in urine and feces through 336 hours postdose accounted for 2.31% and 1.75% of the administered radioactivity, respectively. The bulk of the administered total radioactivity was retained in the rat carcasses through 168, 336, 504, and 840 hours postdose. The kidney cortex, kidney medulla, and liver were the 3 tissues that retained the greatest amounts of the administered radioactivity.

Following a 16.1 µg/kg dose in rats, the plasma concentrations were still quantifiable at 72 hours postdose and the rate of elimination was slow, with $t_{1/2}$ 17.5 hours. It was not possible to accurately define the elimination phase for the 2.67 and 5.28 µg/kg dose levels.

In cynomolgus monkeys, following a single SC dose of ^{14}C-OLP-1002, T_{max} ranged from 0.25 to 1 hour for both total radioactivity and parent compound. Concentrations of total radioactivity were sustained in blood and plasma through the last sampling time of 144 hours postdose. Concentrations of parent compound were sustained in plasma through the last

sampling time of 144 hours postdose in 2 of 3 monkeys, and were similar to plasma total radioactivity concentrations at 8 hours postdose. From 24 to 144 hours postdose, plasma concentrations of total radioactivity were substantially higher than for parent ^{14}C-OLP-1002 plasma concentrations.

The mean C_{max} of parent ^{14}C-OLP-1002 in plasma was 1.96 ng/mL. The mean plasma T_{max} was 0.833 hours. Plasma exposure of parent ^{14}C-OLP-1002 based on AUC extrapolated to infinity ($AUC_{0-\infty}$), was 12.7 ng.h/mL. After reaching C_{max}, plasma concentrations of parent ^{14}C-OLP-1002 declined with a mean $t_{1/2}$ of 84 hours.

1.6. Study Rationale

This is the first time OLP-1002 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data when OLP-1002 is administered SC as single and multiple doses to healthy subjects. This information, together with the pharmacodynamic (PD) and pharmacokinetic (PK) data, will help establish the doses and dosing regimen suitable for future studies in patients. The analgesic effects of OLP-1002 on a capsaicin-induced pain model will also be investigated.

1.7. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. For subjects in the PD assessment groups in Part A there will be some additional discomfort from the capsaicin test. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with OLP-1002 may be found in the Investigator's Brochure[4].

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is to assess the safety and tolerability of single and multiple SC doses of OLP-1002 in healthy subjects.

The exploratory objectives of the study are to evaluate the PD effect of OLP-1002 following single SC doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of single SC doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- incidence and severity of AEs
- vital signs measurements (blood pressure, pulse rate, respiratory rate)
- 12-lead electrocardiogram (ECG) parameters
- incidence of clinical laboratory abnormalities, based on clinical chemistry, hematology, and urinalysis test results
- physical examinations
- injection site assessment.
- demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.

2.2.2. Exploratory Endpoints

The following exploratory objectives will be assessed:

- pain intensity and duration will be assessed by AUC, maximum pain intensity (E_{max}), and time of maximum pain intensity (tE_{max}), calculated using a capsaicin-evoked pain model. The exploratory endpoint of secondary hyperalgesia will be assessed by the area of secondary area of hyperalgesia (Part A only).
- continuous (24-hour) ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval (Part A).
- heat pain threshold measurements and heat pain tolerance measurements.
- For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:

  <u>Primary PK</u>

  - area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])
  - AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)
  - maximum observed plasma concentration (C_{max}) (actual and DN)

  <u>Secondary PK</u>

  - time of the maximum observed plasma concentration (t_{max})
  - apparent plasma terminal elimination half-life ($t_{1/2}$)
- For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:

Primary PK:

- AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)
- $AUC_{0-\infty}$ (actual and DN)
- C_{max} (actual and DN)

Secondary PK

- minimum observed plasma concentration (C_{min})
- t_{max}
- $t_{1/2}$
- observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)
- observed accumulation ratio based on C_{max} (RAC_{max}).
- Temporal change parameter (TCP)

Other PK parameters may also be added if deemed necessary.

3. INVESTIGATIONAL PLAN

This will be a double-blind, randomized, placebo-controlled, single and multiple SC dose study conducted in 2 parts.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, sequential-group design. Overall, 68 healthy subjects will be studied in 11 groups.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, A6, A9, A10, and A11 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 10 (216 hours postdose) from the lower dose levels. For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.

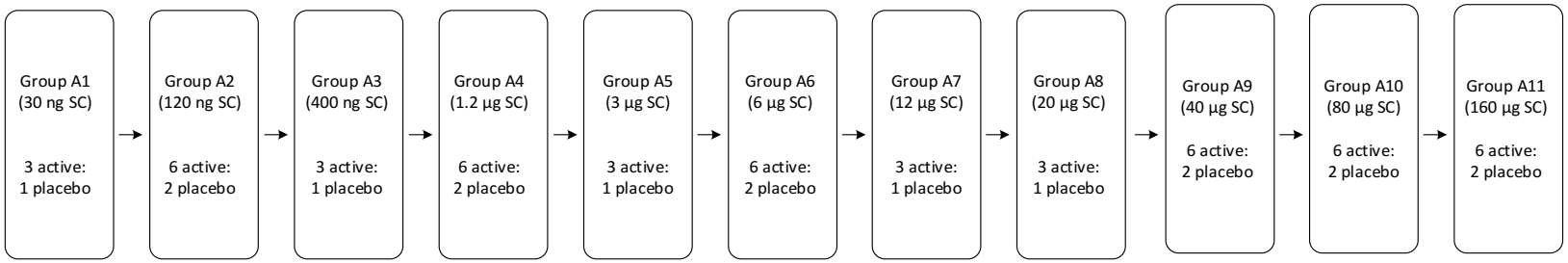
In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, A6,

A9, A10, and A11 will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.

Sentinel dosing will be employed for all groups in Part A. To maintain the blind in a 4-subject group, the first subject will be dosed 48 hours before the second subject, and the second subject will be dosed 48 hours prior to the third and fourth subjects. In PD assessment groups, 2 subjects (1 active: 1 placebo) will be dosed 48 hours before the remaining 6 subjects (5 active: 1 placebo).

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic (Part A)



Active = OLP-1002; SC = subcutaneous.
Six groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

3.1.2. Part B

Part B will comprise a multiple-dose, sequential-group study. Overall, 32 subjects will be studied in 4 groups (Groups B1 to B4), with each group consisting of 8 subjects. Up to 2 additional groups (16 subjects in total) may be included for further assessment of safety and tolerability (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15.

All subjects will return for non-residential visits on Days 18 (± 2 days), 22 (± 2 days), 25 (± 2 days), and 29 (± 2 days), and for a poststudy visit on Day 57 (± 2 days).

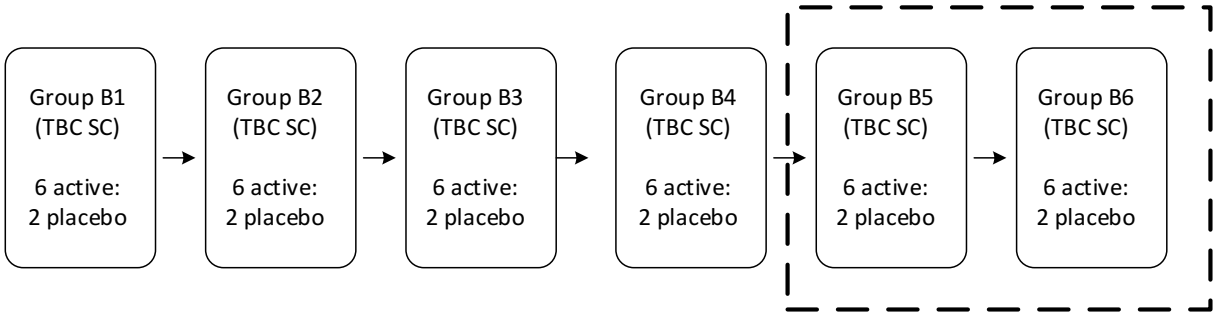
In each of Groups B1 to B4, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from the lower dose levels. Part B may start after a review of the safety, tolerability, and available PK for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

An overview of the study design is shown in Figure 2.

Figure 2: Study Schematic (Part B)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
All doses will be confirmed based on results of Part A and previous groups in Part B.
Groups B5 and B6 will be included if required.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 12 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Start of Study and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, PK, and PD data (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7]), additional dose groups may be added to the study.

Up to 2 additional groups of 8 subjects (6 active: 2 placebo) may be included in Part B. The requirement for additional groups will be agreed with the Sponsor and documented in the Trial Master File (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential-group, ascending-dose design has been chosen for safety reasons as OLP-1002 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Subcutaneous doses have been chosen for both parts of the study, as this is the intended clinical route of administration.

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of

safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 6 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses < 12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. Additional optimization of the PK analysis has delivered an LLOQ of around 1 ng/mL with the limit of detection being 0.2 ng/mL. Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore, if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.

This study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to

assess whether any observed effects are treatment-related or simply reflect the study conditions.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Continuous ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing in Part A for groups consisting of 4 subjects will be such that there will be 48 hours between the first and second subjects, and 48 hours between the second and remaining 2 subjects in each group. For groups in Part A consisting of 8 subjects, 2 subjects (1 active: 1 placebo) will be dosed 48 hours prior to the remaining 6 subjects.

In Part B, sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.

In Parts A and B, there will be a minimum interval of a 10-minute gap between dosing subjects (when dosed on the same day). Continuation to dose the remaining subjects in a group will be at the Investigator's discretion.

3.4.2. Pharmacodynamic Assessment

Pharmacodynamic assessments will be conducted for subjects in Groups A2, A4, A6, A9, A10, and A11.

Human experimental pain models using healthy volunteers can be used to assess the effect of a drug or treatment under controlled clinical conditions. Capsaicin is a vanilloid responsible for the pungent taste of hot peppers. In mammalian species, capsaicin-induced pain is mediated through Group C nerve fibers following activation of vanilloid 1 transient receptor potential (TRPV1) channels[5]. $Na_v1.7$ has been implicated in controlling neuropeptide release from C-fibers, and suppression of capsaicin-induced neurogenic flair has been demonstrated by an $NA_v1.7$ inhibitor[6].

Several studies have used intradermal capsaicin for human experimental pain studies[7,8]. It has been possible to demonstrate dose-dependent responses, with intradermal injections of

100 µg generally agreed to be the ideal dosage for these studies. Intradermal injection of capsaicin causes a brief stinging/burning pain at the injection site (spontaneous pain) followed by development of secondary hyperalgesia, which can be assessed using equipment such as Von Frey hairs. A study by Gazerani et al.[5] found that the response was site-specific and while peak pain intensity and duration were greatest in the forehead it was found that areas of visible flare and secondary hyperalgesia were significantly larger in the forearm, making the forearm the most suitable site for experimentation.

Covance CRU, Leeds, UK in 2009 performed a validation study using intradermal capsaicin (Covance CRU Study: 9999-004) with between-subject and within-subject variability demonstrating that the assessments can be reliably conducted to assess pharmacological response.

For these reasons, it has been decided to:

- Measure both capsaicin-evoked pain and secondary hyperalgesia.
- Limit the number of capsaicin tests to 3 for each subject (pre-screening, baseline, and 48 hours postdose)
- Exclude subjects who have pain <3 or >9 (using a Visual Analogic Scale [VAS]) at the pre-screening visit from PD assessment groups.

3.5. Selection of Doses in the Study

3.5.1. Starting Dose

The rat has been identified as the most sensitive species in a 13-week SC toxicity study with a 4-week recovery phase (Covance study no. 8355564). The NOAEL was the 100 nmol/kg/dose (462.29 µg/kg/dose). This dose level resulted in C_{max} of 27.6 ng/mL and 24.9 ng/mL in males and females, respectively, and AUC_{0-24} of 174 ng.h/mL and 128 ng.h/mL in males and females, respectively[4]. As the exposure was lower in the female rats these data have been used to calculate the safety margins.

The dose of 462.29 µg/kg/dose corresponds to human equivalent doses (HEDs) of 74.8 µg/kg/dose, which gives a maximum recommended starting dose (MRSD) of 444 µg for a 60-kg human and thus a 15000-fold safety margin to the proposed starting dose of 30 ng and 2.8-fold margin to the proposed maximum daily dose of 160 µg. Additionally the NOAEL dose in the cynomolgus monkey was identified as 100 nmol/kg/dose (462.29 µg/kg/dose), which gives a higher HED of 150 µg/kg/dose.

In vivo, doses of 10 pmol/kg/dose (0.0462µg/kg/dose) or less were found to inhibit peripheral acute inflammatory pain. The equivalent human dose for a 60-kg human is 44 ng, thus a dose at which minimal biological effect is anticipated has been selected as the starting dose of 30 ng.

Based on further in vivo studies in the rat (see Section 1.2.2), single doses of 10,000 pmol/kg (10 nmol/kg/dose; 46.2 ug/kg/dose) or less were found to inhibit FCA-induced inflammatory pain and there were no clinically adverse findings. The equivalent dose for a 60-kg human is 44 µg, and this is therefore a dose at which biological effect is anticipated.

3.5.2. Exposure

Human exposures have been estimated from the pharmacokinetics in the cynomolgus monkey since a non-human primate represents the most closely related species. Approximately dose-proportional exposure was seen in the 13-week toxicity study (Covance study no. 8355565) and ^{14}C pharmacokinetic study (Covance study no. 8355568) over a dose range of approximately 1.1 to 100 nmol/kg (5.06 to 462.29 µg/kg)[4]. However, the lowest dose (5.06 µg/kg) from the ^{14}C study has been used to estimate the human exposures as it is closest to the proposed human dose range and has the sufficient quantifiable data.

The assumptions made in the human exposure estimation were that human exposure would be similar to the cynomolgus monkey and that exposure would be linear with dose. Following a dose of 5.06 µg/kg in the cynomolgus monkey, the C_{max} was 1.96 ng/mL and $AUC_{0-\infty}$ was 12.7 ng.h/mL. The extrapolated exposures at the planned human doses are shown in Table 1 with margins calculated to the exposures at the NOAEL in the female rat.

Table 1: Estimated Human Exposure and Safety Margins to the NOAEL in the Female Rat for Single Dose Administration of OLP-1002

Human dose		Single dose to human		Safety margins for single dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\infty}$
0.03	0.000500	0.000194	0.00125	129000	102000
0.12	0.00200	0.000775	0.00502	32100	25500
0.4	0.00667	0.00258	0.0167	9640	7650
1.2	0.0200	0.0077	0.0502	3210	2550
3	0.0500	0.0194	0.125	1290	1020
6	0.100	0.0387	0.251	643	510
12	0.200	0.0775	0.502	321	255
20	0.333	0.129	0.837	193	153
40	0.667	0.258	1.673	96	76
80	1.333	0.516	3.347	48	38
160	2.667	1.033	6.693	24	19

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

The dosing interval currently anticipated for the multiple-ascending-dose part of this study is 72 hours or 96 hours. Thus the average dosing interval (82 hours) is similar to the half-life determined in the monkey ^{14}C study of 84 hours. Dosing at approximately once per half-life would be anticipated to result in accumulation of around 2-fold. However, higher levels of accumulation were observed (2.28-fold for C_{max} and 3.76-fold for AUC_{0-24}) on Day 88 at the top dose group (100 nmol/kg, 462.28 µg/kg) in the 13-week cynomologus monkey toxicity study following twice-weekly dosing (every 72 or 96 hours). Calculations were performed to estimate the likely human half-life using a standard 1-point allometric approach from the ^{14}C cynomolgus monkey pharmacokinetic study data. The exponents used were 0.75 for apparent total plasma clearance (CL/F) and 1 for apparent volume of distribution (V_z/F) values combined with the average body weight of the animal (3.1 kg) and scaling to a 60 kg human [9–11]. This resulted in a human half-life estimate of 180 h which in turn gave an accumulation

estimate of 3.7-fold based upon a dosing interval of 82 h. This further supports the use of the greater than 2-fold accumulation from the 13-week cynomolgus study to estimate exposure following multiple dosing. Multiplication of the exposure estimates for the single ascending dose by 2.28 for C_{max} and 3.76 for AUC resulted in exposure estimates for multiple dosing presented in Table 2.

Table 2: Estimated Human Exposure and Safety Margin to the NOAEL in the Female Rat for Multiple Dose Administration of OLP-1002

Human dose		Multiple dose to human		Safety margins for multiple dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\tau,ss}$
0.03	0.000500	0.000442	0.00472	56000	27000
0.12	0.00200	0.00177	0.0189	14100	6800
0.4	0.00667	0.00589	0.0629	4230	2030
1.2	0.0200	0.017663	0.189	1410	680
3	0.0500	0.0442	0.472	560	270
6	0.100	0.0883	0.944	282	136
12	0.200	0.177	1.89	141	68
20	0.333	0.294	3.15	85	41
30	0.500	0.442	4.72	56	27
40	0.667	0.589	6.29	42	20

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

3.5.3. Proposed Doses

The proposed IMP dose levels for Parts A and B are shown in Table 3.

Table 3: Proposed Investigational Medicinal Product Dose Levels for Parts A and B

Study Part	Group	Dose (OLP-1002)
Part A	A1	30 ng or placebo
	A2	120 ng or placebo
	A3	400 ng or placebo
	A4	1.2 µg or placebo
	A5	3 µg or placebo
	A6	6 µg or placebo
	A7	12 µg or placebo
	A8	20 µg or placebo
	A9	40 µg or placebo
	A10	80 µg or placebo
	A11	160 µg or placebo
Part B	B1	TBC or placebo
	B2	TBC or placebo
	B3	TBC or placebo
	B4	TBC or placebo
	B5*	TBC or placebo
	B6*	TBC or placebo

Abbreviations: TBC = to be confirmed
* groups to be included if required.

In Parts A and B, there should not be an increase of > 3-fold between dose levels above 120 ng.

Since predictions of human exposure of OLP-1002 suggest that OLP-1002 concentrations may be not be quantifiable and human data have been estimated from a single species, it is proposed that the highest dose in the multiple-ascending-dose part will be up to 50% of the highest dose in the single-ascending-dose part (ie, if the highest dose in the single-ascending-dose part is 160 µg, the highest dose in the multiple-ascending-dose part will be 80 µg). Therefore, if the predicted accumulation of 3.7-fold occurs, the highest exposure in Part B will not exceed ~2-fold the maximum exposure in the single-ascending-dose part.

Group B4 may be dosed concurrently with Group A10 (80 µg), following the dose escalation meeting for Group A9 (40 µg). The predicted C_{max} and $AUC_{0-\infty}$ for a single dose of 40 µg are 0.258 ng/mL and 1.673 ng.h/mL, respectively (Table 1). Assuming 3.7-fold accumulation, the predicted C_{max} and $AUC_{0-\infty}$ at the 20 µg dose level in Group B4 are 0.294 ng/mL and 3.15 ng.h/mL, respectively (Table 2). Exposure in Group B4, therefore, is not predicted to exceed ~2-fold the maximum exposure in Group A9.

If additional groups (B5 and B6) are required, the predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

3.6. Dose Escalation

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 10 (216 hours postdose) from groups that received lower doses of OLP-1002. For escalation to doses ≥ 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, A6, A9, A10, and A11) have been reviewed from the previous lower dose group, such that data from a minimum of 3 or 4 subjects, respectively, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

The justification for this is as follows:

- The study drug is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.
- A minimum of 3 subjects receiving the active drug is considered sufficient to characterize the safety profile for OLP-1002.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarizing results from all available safety assessments, will be sent to the Sponsor and a dose-escalation meeting will occur prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PD data may also be reviewed on an ongoing basis. In the event of a disagreement between Sponsor and Investigator on the dose-escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- One or more subjects experience an SAE that is considered to be related to OLP-1002.

- Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase (defined as 3 times the upper limit of normal), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥ 1 subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- Systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng.h/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).

If the sponsor deems it appropriate to resume dosing after the internal safety review, it can be done after the approval of a substantial protocol amendment.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Healthy male or females of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) between 18.0 and 28.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, single 12-lead ECG (resting heart rate > 45 bpm and < 90 bpm), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening as assessed by the Investigator (or designee).
4. Willing to abide by the contraception requirements as detailed in Appendix 4.

5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Any of the following:
    - QTcF > 450 ms confirmed by repeat measurement.
    - QRS duration > 110 ms confirmed by repeat measurement.
    - PR interval > 220 ms confirmed by repeat measurement.
    - findings which would make QTc measurements difficult or QTc data uninterpretable.
    - history of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
4. Female subjects who are pregnant or breastfeeding.
5. History of alcoholism or drug/chemical abuse within 1 year prior to Screening.
6. Alcohol consumption of > 21 units per week for males and >14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
7. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
8. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2).
9. Active skin conditions such as dermatitis, allergy, eczema, psoriasis, or abnormal healing.
10. Tattoos, scars, or moles that in the opinion of the Investigator are likely to interfere with dosing or study assessments at any of the potential injection sites.
11. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days or 5 half-lives of the investigational product, whichever is longer, prior to Check-in.
12. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John’s wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).

13. Use or intend to use any prescription medications/products other than hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptive concomitant medications within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
15. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and/or Sponsor have given their prior consent.
16. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in.
17. Receipt of blood products within 60 days prior to Check-in.
18. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
19. Poor peripheral venous access.
20. Have previously completed or withdrawn from this study or any other study investigating OLP-1002, and have previously received the investigational product.
21. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
22. Part A – PD assessment groups only
    - Subjects considered non-acceptable responders to the intradermal capsaicin test at screening, defined as maximum VAS score of < 3.0 or > 9.0.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number at the time of their randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A, Subjects 101, 102, etc., in Part B Subjects 201, 202, etc.). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal, including:
    - a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),
    - severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),
    - elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),
    - QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),
    - Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),
    - Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Vials of OLP-1002 Injection Solution 100 μg/mL (1.5 mL in 5-mL vials) and the Diluent for OLP-1002 Injection Solution (5 mL in 10-mL vials) will be supplied by the Sponsor, along with the batch/lot number and Certificate of Analysis. The Diluent for OLP-1002 Injection Solution will also be used as the Placebo formulation. A certificate of batch certification and release, authorized by a Qualified Person in the European Union (EU) will also be issued, by a Covance CRU Qualified Person, for each batch of IMP imported into the EU.

The IMPs will be stored according to the instructions on the label at the CRU in a location that is locked with restricted access.

Dose solutions (OLP-1002 Injection Solution diluted with the Diluent for OLP-1002 Injection Solution) will be prepared by Covance CRU Pharmacy staff in accordance with instructions provided in the Pharmacy Manual. The Placebo formulation will be the Diluent for OLP-1002 Injection Solution without further manipulation.

5.2. Study Treatment Administration

Subjects will be administered the IMP in numerical order. OLP-1002 will be administered by SC injection in the upper arm. If subcutaneous dosing of OLP-1002 in the upper arm is not possible, the subject may be dosed in the abdomen at the Investigator's discretion. For subjects in Groups A2, A4, A6, A9, A10, and A11, dosing will be on the opposite arm to the intradermal capsaicin test. At dose levels of ≥40 μg (Groups A9, A10, and A11), doses may be administered as multiple SC injections in the same location (ie, 2 SC injections in the upper arm).

5.3. Randomization

The randomization code will be produced by the statistics department at Covance using a computer-generated pseudo-random permutation procedure. In Part A, 1 subject in groups consisting of 4 subjects, and 2 subjects in groups consisting of 8 subjects, will be randomly assigned to receive placebo. In Part B, 2 subjects per group will be randomly assigned to receive placebo. All other subjects in a group will be randomized to receive OLP-1002.

Prior to the start of the study, a copy of the master randomization code will be supplied into the Covance CRU pharmacy staff (in sealed envelopes).

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo solution will be identical in appearance to the OLP-1002.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

To maintain the blind, the Investigator will be provided with sealed randomization code-break envelopes for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose-escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

All doses of IMP will be administered by suitably qualified study site staff.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription medications/products from 14 days prior to dosing until the Follow-up visit, and non-prescription medications/products from 7 days prior to dosing until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests. On dosing days, subjects will receive a light breakfast approximately 2 hours prior to dosing. Meals will be provided as appropriate at other times and water will be freely available at all times.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until the Follow-up visit.

Xanthine-containing foods and beverages will not be allowed from 36 hours before Check-in until Discharge from the site. Xanthine-containing foods and beverages will also not be allowed form 36 hours before non-residential site visits.

Chilli pepper/hot sauce will not be allowed for 48 hours prior to Check-in for all subjects. Subjects in Groups A2, A4, A6, A9, A10, and A11 will not be allowed chilli pepper/hot sauce for 48 hours prior to their pre-screening visit.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until Discharge. Following discharge, up to 2 units/day of alcohol are permitted until 36 hours before each non-residential visit and the Follow-up visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 3 days before Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit. Subjects should not be in receipt of blood products for 60 days prior to check-in.

6.6. Other Restrictions

Subjects in Groups A2, A4, A6, A9, A10, and A11 will not be allowed to shower within 1 hour prior to the capsaicin-evoked pain tests at prescreening, predose, and postdose.

Subjects will not be allowed to apply moisturizing creams or oils to the dosing site within 1 hour prior to dosing, or to the assessment site within 1 hour prior to the capsaicin-evoked pain test.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- vital signs
- blood samples
- cardiac monitoring/ECG extractions
- any other procedures.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, PK analysis will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Pharmacodynamic Assessments

Capsaicin intradermal test will be performed for subjects in Groups A2, A4, A6, A9, A10, and A11. Each subject will be tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).

7.2.1. Capsaicin-evoked Pain Model

The capsaicin model will be conducted by intradermal injection of capsaicin (100 µg in 100 µL of sterile saline containing 8% [w/w] Tween 80) into the skin of the anterior aspect of the forearm, midway between the elbow and the wrist. The bleb area (wheal) will be a sign of local plasma extravasation. An assessment of the pain intensity related to capsaicin injection will be estimated by repeated use of a VAS from injection to 5 minutes post-injection or until the pain intensity returned to zero. The AUC, E_{max}, and tE_{max} will be calculated and reported using dedicated software.

7.2.2. Secondary Hyperalgesia

The area of secondary hyperalgesia will be quantified with a 60-g weighted von Frey hair, by stimulating along 8 linear paths (4 vectors crossing at the location of the injection site) arranged vertically and horizontally around the stimulation site in 5-mm steps (starting approximately 6 cm away from the injection site). The area of secondary hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection.

7.3. Safety and Tolerability Assessments

Safety and tolerability assessments will be conducted at the times indicated in the Schedule of Assessments (Appendix 6). Timepoints may be adjusted based on an ongoing review of the data, and additional assessments may be conducted if deemed necessary by the Investigator or designee.

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a follicle-stimulating hormone (FSH) test and pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

Subjects must be supine for at least 5 minutes before blood pressure, pulse rate, and respiratory rate measurements.

7.3.4. Electrocardiogram

7.3.4.1. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value > 500 msec
- QTcF change from the mean baseline (Day 1 predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.4.2. Continuous (24-hour) Electrocardiogram

At the times indicated in the Schedule of Assessments (Appendix 6), continuous (24-hour) ECGs will be performed.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint. Each extraction will last for 5 minutes. Environmental distractions (eg, television, playing games, radio, conversation) should be avoided during the pre-ECG time window.

Continuous 24-hour ECGs are not planned for Part B of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.3.5. Heat Pain Threshold Test

Heat pain threshold tests will be conducted at the times indicated in the Schedule of Assessments (Appendix 6).

A computer-controlled thermal sensory analyzer device will be used to measure the heat pain threshold and tolerance level of the subjects. The heat pain assessments will be conducted on the subject's thigh.

Heat Pain Threshold:

For heat pain threshold measurements, the thermode will be placed directly on the skin of the right thigh, within an area selected before the start of the experiment and defined by surgical marking. The thermode will have a baseline temperature of 32°C, and will be programmed to gradually increase at a rate of 1.0°C per second. The subject will be given a controller in their dominant hand, to indicate when the heat pain threshold (first sensation of heat pain) is reached by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Heat Pain Tolerance:

For heat pain tolerance measurements, the thermode will be placed within the same surgically marked skin area of the anterior side of the right thigh, which was used to assess heat pain threshold. The thermode will have a baseline temperature of 32°C, and will be programmed

to gradually increase at a rate of 1.0°C per second. The subject will be given a controller in their dominant hand, to indicate when the heat-evoked pain has reached an intensity that is no longer tolerable, by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Safety Precautions

As there is a risk that OLP-1002 may affect the heat pain threshold, Covance CRU will put appropriate safety measures in place to ensure that subjects are not exposed to extremes of temperature when taking a shower or consuming hot drinks. During the heat pain safety assessments, the cut-off temperature for either test is 53°C in order to prevent skin injury.

7.3.6. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

7.3.7. Body Weight and Height

Body weight (in underclothes) and height will be recorded at the times indicated in the Schedule of Assessments in Appendix 6. BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{body weight (kg)}}{(\text{height [m]})^2} \quad (\text{kg/m}^2)$$

7.3.8. Injection Site Assessments

Injection site assessments will be made at the times indicated in the Study Plan (Appendix 6).

Assessments will involve evaluation of the dosing site for the following criteria:

- Pain will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Requires medical intervention greater than analgesia

- Redness will be assessed by estimating the size of the red patch at the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm	51-100 mm	More than 100 mm	Requires medical intervention greater than analgesia

• Swelling will be assessed by estimating the size of the raised area around the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm and does not interfere with activity	51-100 mm or interferes with activity	More than 100 mm and prevents daily activity	Requires medical intervention greater than analgesia

In addition, how the swelling affects the subject in their daily routing activities will be considered.

• Tenderness will be evaluated using the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Mild pain to touch	Moderate Pain to touch	Severe pain to touch	Requires medical intervention greater than analgesia

• Bruising and ulceration will be evaluated as being present or absent.

Local tolerability ratings of ≥Grade 3 and the presence of ulceration will be recorded as an adverse event.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. As part of Protocol Version 5, 3 additional groups will be included in Part A (Groups A9, A10, and A11) and 1 additional group will be included in Part B (Group B4). Up to 2 additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.2. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

8.4. Pharmacodynamic Analyses

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned.

8.5. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- Mild: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but posing no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- Not Related: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- Unlikely Related: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- Related: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at the Follow-up visit will be followed up, where possible,

until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit (CRU). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Covance Drug Safety Services (DSS) Europe, Maidenhead, UK are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to DSS and the Sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Covance DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 2 working days of the initial notification to DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy reported by female subjects or

the female partners of male subjects should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total protein Urea	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[a]:	**Drug screen[b]:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test MDMA Alcohol breath test	Follicle-stimulating hormone[a] Serum pregnancy test (human chorionic gonadotropin)[a] Urine pregnancy test[c]

[a] Only analyzed at Screening.
[b] Only analyzed at Screening and Check-in.
[c] A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	19	76
Clinical laboratory evaluations (excluding serology)	7.5	6	45
Serology	3.5	1	3.5
Total:			124.5

Part B

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	29	116
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			194.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject during the study will not exceed that donated during a standard blood donation (approximately 500 mL).

Appendix 4: Contraception Guidance

Definitions

Females of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Females of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary (non-barrier) methods of contraception include:

- hormone injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - bilateral tubal ligation
    - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)

- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects can only choose a cervical cap or diaphragm if they have already had a prescription and fitting by their healthcare provider to ensure protocol requirements are met. Female subjects of childbearing potential should refrain from donation of ova from Check-in until 90 days after the Follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide
- vasectomised male subject (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success).

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the Follow-up visit.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the Follow-up visit.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a

public registry, all identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled and randomized subject, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

Study Plan – Part A (Single Dose)

	Pre-screening [d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Urine drugs of abuse screen		X	X							
Alcohol breath test		X	X							
Cotinine test		X	X							
Serology		X								
FSH and serum pregnancy test[a]		X								
Urine pregnancy test[a]			X							X
Informed consent	X	X								
Study residency:										
Check-in			X							
Check-out					Day 3 (48 hours postdose)					
Non-residential visit	X	X				X	X	X	X	X
Study drug administration:					Day 1 (0 hours)					
Safety and tolerability:										
Adverse event recording		X	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording		X	X	X	Ongoing	X	X	X	X	X

	Pre-screening [d]	**Screening**	**Day -2**	**Day -1**	**Days 1 to 3**	**Day 4**	**Day 7 (± 2 days)**	**Day 10 (± 2 days)**	**Day 14 (± 2 days)**	**Poststudy (Day 28 ± 2 days)**
Supine blood pressure, pulse rate, respiratory rate, and body temperature		X			Predose, 1, 2, 4, 8, 24 (± 1 hour), and 48 hours postdose	X	X	X	X	X
Supine 12-lead ECG		X			Predose, 4, 24 (± 1 hour) and 48 hours postdose		X		X	X
Continuous ECG extraction[b,c]				-24, -23.5, -23, -22.5, -22, -21.5, -21, -20, -18, -16, -12 hours	Day 1: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours					
Heat pain threshold test (heat pain threshold and heat pain tolerance)					Day 1: predose, 2, 4, 12, and 24 hours postdose (± 1 hour)					
Clinical chemistry, haematology, and urinalysis		X	X		48 hours postdose		X		X	X

	Pre-screening [d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Height and BMI		X								
Body weight		X	X							X
Physical examination		X								
Symptom-directed physical examination					Prior to discharge		X		X	X
Injection site assessment					Predose, 1, 2, 4, 8, 24, 48 hours postdose		X		X	X
Pharmacokinetics[e]										
Blood sampling					Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose	X	X	X	X	X
Pharmacodynamics[d]:										
Intradermal capsaicin test (capsaicin-evoked pain and secondary hyperalgesia measurement)	X		X		Day 2 (The area of secondary area of hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection)					

Abbreviations: BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone.
[a] Female subjects only; a positive urine pregnancy test result will be confirmed with a serum pregnancy test.
[b] All times are relative to dosing with OLP-1002.
[c] Continuous ECG recording may begin at approximately 25 hours before dosing to allow for checks to be completed prior to the first extraction timepoint and will continue for 24 hours postdose, ie, until after the last timepoint for ECG extraction (24 hours postdose). At timepoints for ECG extractions, subjects will be supinely resting for a total of 15 minutes (10-minute supine rest period, 5-minute extraction). Data will be archived for potential future analysis and will not be available for review during the study.
[d] Pharmacodynamic assessment groups only.
[e] PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

Study Plan – Part B (Multiple Dose)

	Screening	Day -1	Days 1-15	Day 18 (± 2 days)	Day 22 (± 2 days)	Day 25 (± 2 days)	Day 29 (± 2 days)	Poststudy (Day 57 ± 2 days)
Inclusion/exclusion criteria	X							
Demographic data	X							
Medical history	X							
Urine drugs of abuse screen	X	X						
Alcohol breath test	X	X						
Cotinine test	X	X						
Serology	X							
FSH and serum pregnancy test[a]	X							
Urine pregnancy test[a]		X			X		X	X
Informed consent	X							
Study residency:								
Check-in		X						
Check-out			Day 15 (48 hours postdose)					
Non-residential visit	X			X	X	X	X	X
Study drug administration:			Days 1, 4, 7, 10, and 13					
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature	X		Day 1: predose, 1, 2, 4 and 8 hours postdose Day 2, Day 4 (postdose), Day 5, Day 7 (postdose), Day 9, Day 10 (postdose), Day 12, Day 13: predose, 1, 2, 4 and 8 hours postdose, and Day 15	X	X	X	X	X

	Screening	Day -1	Days 1-15	Day 18	Day 22	Day 25	Day 29	Poststudy (Day 57 ± 2 days)
Heat pain threshold test (heat pain threshold and heat pain tolerance)	X		Day 1 and Day 13: predose, 1, 2, 4, 8, 24 hours postdose					
Supine 12-lead ECG	X		Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Clinical chemistry, haematology, and urinalysis	X	X	Days 2, 5, 9, 12, 17		X		X	X
Height and BMI	X							
Body weight	X	X						X
Physical examination	X							
Symptom-directed physical examination			Days 1, 4, 7, 10, 13		X		X	X
Injection site assessment			Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Pharmacokinetics:								
Blood sampling[b]			Day 1 and Day 13: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose Days 4, 7, 10 Predose Day 15	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone.
[a] Female subjects only; a positive urine pregnancy test results will be confirmed with a serum pregnancy test.
[b] PK timepoints will be reviewed based on emerging data and may be updated.

Appendix 7: Protocol Amendment Summary of Changes

Protocol Amendment 6 (Version 5; 27 September 2019)

This substantial amendment has been issued to increase the maximum dose in this study, which will be administered in 3 additional groups to Part A (Groups A9, A10, and A11), and 1 additional group to Part B (Group B4). Further non-clinical data on the ability of OLP-1002 to reverse inflammatory allodynia induced by the FCA model in rats have also been included in Section 1, and the project physician has been updated.

For the additional groups, the maximum administered dose in this study will exceed the previously stated maximum dose of 20 µg. The justification for this is as follows:

- The NOAEL for a 60-kg human has 96- and 76-fold safety margins to the C_{max} and $AUC_{0-\infty}$, respectively, for the proposed additional single dose of 40 µg (Group A9), 48- and 38-fold safety margins to the C_{max} and $AUC_{0-\infty}$, respectively, for the proposed additional single dose of 80 µg (Group A10), respectively, and 24- and 19-fold safety margins to the C_{max} and $AUC_{0-\infty}$, respectively, for the proposed additional single dose of 160 µg (Group A11), respectively.

- Single doses of OLP-1002 up to 20 ug have been safe and well tolerated in Groups A1 to A8.

- The NOAEL for a 60-kg human has 42- and 20-fold safety margins to the C_{max} and $AUC_{0\text{-tau ss}}$, respectively, for the proposed dose for Group B4 of 5 x 20 µg. Based on the predicted accumulation of 3.7-fold, this dose level will not exceed the NOAEL.

- In vivo, single dose of 10,000 pmol/kg (10 nmol/kg/dose; 46.2 µg/kg/dose) or less were found to inhibit FCA-induced inflammatory pain and there were no clinically adverse findings. The equivalent dose for a 60-kg human is 44 µg, which is therefore a dose at which biological effect is anticipated.

- Predicted safety margins for C_{max} and $AUC_{0-\infty}$ (Part A) and $AUC_{0\text{-tau, ss}}$ (Part B) for the new groups are deemed to be acceptable (see Table 1 and Table 2).

A detailed summary of changes is presented below. Deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**. Additionally, the synopsis was updated to reflect changes to the body of the protocol, the table of contents and list of tables and figures were updated, the date and version number were updated, and minor editorial corrections were made.

Change	Justification
Study Identification Project physician updated from [redacted] to [redacted]	Updated due to a change in study personnel.

Change	Justification
Section 1.2.2 When evaluated for their ability to reverse the inflammatory pain in rats inflicted with Freund's Complete Adjuvant (FCA)-induced severe paw inflammation, OLP-1002 at 300 pmol/kg and OLP-1002R at 100 pmol/kg significantly reversed the thermal hyperalgesia, and both were more effective than pregabalin 30 mg/kg. **Two further studies investigating OLP-1002R at concentrations up to 10,000 pmol/kg using the FCA model showed a reversal of inflammatory allodynia in rats. Both studies demonstrated that maintenance of a steady state of efficacy over time was dose dependent, with the dose of 100 pmol/kg being sufficient over 1 day/30 hours postdose, and the higher doses of 1000 pmol/kg and 10,000 pmol/kg being the most suitable up to 3 days/96 hours postdose. Assuming that thermal withdrawal latency time of the normal control group was equivalent to 100% allodynia inhibition and that of the negative control group was equivalent to 100% allodynia induction, allodynia inhibition efficacy by OLP-1002R was estimated to be 20.65% ~ 45.48% and 34.21% ~ 58.72 % in the 2 studies. During both studies, no abnormalities or clinical findings were observed.**	New non-clinical data added to justify the therapeutic dose for OLP-1002.
Section 3.1.1 Part A will comprise a single-dose, sequential-group design. Overall, ~~44~~**68** healthy subjects will be studied in ~~8~~**11** groups. ~~Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, PK, and PD (Section 3.3).~~ Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, ~~and~~ A6~~,~~ **A9, A10, and A11** will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2). Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days). Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days). Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 10 (216	Text updated to include Groups A9, A10, and A11.

Change	Justification
hours postdose) from the lower dose levels. For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation. In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, ~~and~~ A6~~,~~ **A9, A10, and A11** will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.	
Figure 1 **Figure updated to include Groups A9, A10, and A11.** ~~Groups A9 to A11 may be included if required; dose levels will not exceed the maximum proposed dose of 20 µg~~. ~~Three~~ **Six** groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).	Figure and footnote updated based on the change in maximum dose, and the inclusion of Groups A9, A10, and A11.
Section 3.1.2 Part B will comprise a multiple-dose, sequential-group study. Overall, ~~24~~**32** subjects will be studied in ~~3~~**4** groups (Groups B1 to B~~3~~**4**), with each group consisting of 8 subjects. Up to ~~3~~**2** additional groups (~~24~~**16** subjects in total) may be included for further assessment of safety and tolerability (Section 3.3). Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15. All subjects will return for non-residential visits on Days 18 (± 2 days), 22 (± 2 days), 25 (± 2 days), and 29 (± 2 days), and for a poststudy visit on Day 57 (± 2 days). In each of Groups B1 to B~~3~~**4**, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.	Text updated to include Group B4.
Figure 2 **Figure updated to include Group B4.** All doses will be confirmed based on results of Part A~~; dose levels will not exceed the maximum proposed dose of 20 µg~~ **and previous groups in Part B.** Groups B4**5** ~~to~~ **and** B6 will be included if required.	Figure and footnote updated based on the change in maximum dose, and the inclusion of Group B4.
Section 3.3 ~~The maximum dose for any additional group will not exceed 20 µg. Up to 3 further groups of 8 subjects (6 active: 2 placebo) may be included in Part A, and~~ ~~u~~**U**p to ~~3~~**2** additional groups of 8 subjects	Text updated following inclusion of Groups A9, A10, A11, and B4.

Change	Justification
(6 active: 2 placebo) may be included in Part B. The requirement for additional groups will be agreed with the Sponsor and documented in the Trial Master File (TMF).	
Section 3.4 In order to assess the PD effects of OLP-1002, ~~3~~**6** groups in Part A will include 8 subjects (6 active; 2 placebo).	Text updated following the inclusion of Groups A9, A10, and A11.
Section 3.4 ~~A could potentially~~**Additional optimization of the PK analysis has** deliver**ed** an LLOQ of around 0.1 ng/mL **with the limit of detection being 0.2 ng/mL**.	Added to include information regarding developments in the PK analysis of OLP-1002.
Section 3.4.2 Pharmacodynamic assessments will be conducted for subjects in Groups A2, A4, ~~and~~ A6**, A9, A10, and A11**.	Text updated following the inclusion of Groups A9, A10, and A11.
Section 3.5.1 The dose of 462.29 µg/kg/dose corresponds to human equivalent doses (HEDs) of 74.8 µg/kg/dose, which gives a maximum recommended starting dose (MRSD) of 444 µg for a 60-kg human and thus a 15000-fold safety margin to the proposed starting dose of 30 ng and ~~22~~**2.8**-fold margin to the proposed maximum **daily** dose of ~~20~~**160** µg. Additionally the NOAEL dose in the cynomolgus monkey was identified as 100 nmol/kg/dose (462.29 µg/kg/dose), which gives a higher HED of 150 µg/kg/dose. In vivo, doses of 10 pmol/kg/dose (0.0462µg/kg/dose) or less were found to inhibit peripheral acute inflammatory pain. The equivalent human dose for a 60-kg human is 44 ng, thus a dose at which minimal biological effect is anticipated has been selected as the starting dose of 30 ng. **Based on further in vivo studies in the rat (see Section 1.2.2), single doses of 10,000 pmol/kg (10 nmol/kg/dose; 46.2 ug/kg/dose) or less were found to inhibit FCA-induced inflammatory pain and there were no clinically adverse findings. The equivalent dose for a 60-kg human is 44 µg, and this is therefore a dose at which biological effect is anticipated.**	Text updated based on new non-clinical data to specify the anticipated therapeutic dose level in humans.
Table 1 Data for 40 µg, 80 µg, and 160 µg added to table.	Table updated to include data for the increased dose levels in Part A.

Change	Justification
Table 2 Data for 40 µg added to table.	Table updated to include data for the increased dose level in Part B.
Table 3 Dose levels for Groups A9, A10, and A11 added to table.	Table updated following inclusion of Groups A9, A10, and A11.
Section 3.5.3 ~~For Part B, dose levels, dosing frequency, and dosing duration will be decided, in consultation with the Sponsor, on the basis of data from Part A of the study.~~ Since predictions of human exposure of OLP-1002 suggest that OLP-1002 concentrations may be not be quantifiable and human data have been estimated from a single species, it is proposed that the highest dose in the multiple-ascending-dose part will be up to 50% of the highest dose in the single-ascending-dose part (ie, if the highest dose in the single-ascending-dose part is ~~20~~**160** µg, the highest dose in the multiple-ascending-dose part will be ~~10~~**80** µg). Therefore, if the predicted accumulation of 3.7-fold occurs, the highest exposure in ~~the multiple-ascending-dose p~~**P**art **B** will not exceed ~2-fold the maximum exposure in the single-ascending-dose part. **Group B4 may be dosed concurrently with Group A10 (80 µg), following the dose escalation meeting for Group A9 (40 µg). The predicted C_{max} and $AUC_{0-\infty}$ for a single dose of 40 µg are 0.258 ng/mL and 1.673 ng.h/mL, respectively (Table 1). Assuming 3.7-fold accumulation, the predicted C_{max} and $AUC_{0-\infty}$ at the 20 µg dose level in Group B4 are 0.294 ng/mL and 3.15 ng.h/mL, respectively (Table 2). Exposure in Group B4, therefore, is not predicted to exceed ~2-fold the maximum exposure in Group A9.** If additional groups (~~A9-11 or B3-6~~**B5 and B6**) are required, the ~~maximum daily dose administered will not exceed 20 µg and~~ predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.	Justification added for conducting Groups A10 and B4 concurrently.
Section 3.6 For escalation to doses ~~>~~≥ 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.	Updated for consistency with section 3.1.1

Change	Justification
In Part B, doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation. Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, ~~and~~ A6**, A9, A10, and A11**) have been reviewed from the previous lower dose group, such that data from a minimum of 3 or 4 subjects, respectively, who have received OLP-1002 will be used to make the dose-escalation decision.	Text updated following the inclusion of Groups A9, A10, and A11.
Section 3.7 • ~~The dose will not exceed 20 µg or the s~~**S**ystemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng.h/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).	Text updated due to the increased maximum dose level.
Section 5.2 For subjects in Groups A2, A4, ~~and~~ A6**, A9, A10, and A11**, dosing will be on the opposite arm to the intradermal capsaicin test. **At dose levels of ≥40 µg (Groups A9, A10, and A11), doses may be administered as multiple SC injections in the same location (ie, 2 SC injections in the upper arm).**	The highest doses of 40 µg, 80 µg, and 160 µg may be administered as multiple SC injections due to the volume of the dose.
Section 6.2 Chi**l**li pepper/hot sauce will not be allowed for 48 hours prior to Check-in for all subjects. Subjects in Groups A2, A4, ~~and~~ A6**, A9, A10, and A11** will not be allowed chi**l**li pepper/hot sauce for 48 hours prior to their pre-screening visit.	Text updated following the inclusion of Groups A9, A10, and A11.
Section 6.6 Subjects in Groups A2, A4, ~~and~~ A6**, A9, A10, and A11** will not be allowed to shower within 1 hour prior to the capsaicin-evoked pain tests at prescreening, predose, and postdose.	Text updated following the inclusion of Groups A9, A10, and A11.
Section 7.2 Capsaicin intradermal test will be performed for subjects in Groups A2, A4, ~~and~~ A6**, A9, A10, and A11**. Each subject will be	Text updated following the inclusion of Groups A9, A10, and A11.

Change	Justification
tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).	
Section 8.1 No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. **As part of Protocol Version 5, 3 additional groups will be included in Part A (Groups A9, A10, and A11) and 1 additional group will be included in Part B (Group B4).** ~~In order to achieve PD endpoints in Part A, additional subjects will be included in 3 groups (8 subjects in total; 6 active: 2 placebo). Up to 3 additional groups may be added to Part A, consisting of either 4 subjects (3 active; 1 placebo) or 8 subjects (6 active; 2 placebo).~~ Up to ~~3~~**2** additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).	Text updated following the inclusion of Groups A9, A10, A11, and B4.

Protocol Amendment 5 (Version 4; 26 March 2019)

This substantial amendment has been issued to update the Principal Investigator from [redacted] to [redacted].

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**.

Title Page

Principal Investigator:
[redacted] was replaced by [redacted]

Investigator Agreement

[redacted] was replaced by [redacted]

Study Identification

[redacted] was replaced by [redacted]

Tel: [redacted] was replaced by [redacted]

Protocol Amendment 4 (Version 3; 29 January 2019)

This substantial amendment has been issued to update the female contraception criteria to allow female subjects to use alternative forms of contraception including the combined oral contraceptive pill, combined hormonal patch, and combined hormonal vaginal ring. Additionally, it has been clarified that only a serum pregnancy test will be conducted at Screening.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Appendix 4

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary ~~highly effective~~ and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary ~~highly effective~~ **(non-barrier)** methods of contraception include:

- **hormone injection (as prescribed)**
- **combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)**
- **combined hormonal patch (as prescribed)**
- **combined hormonal vaginal ring (as prescribed)**
- surgical method performed at least 3 months prior to the Screening visit:
    - bilateral tubal ligation
    - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)
- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Appendix 6

~~Hormone panel~~ was replaced by **FSH and serum pregnancy test** in the study plan for Part A and Part B for clarity.

A footnote was added to the study plan for Part A and Part B to specify that the FSH and serum pregnancy test will be conducted for female subjects only.

Urine pregnancy test at Screening removed for Part A and Part B.

Protocol Amendment 3 (Version 2.2; 12 December 2018)

This non-substantial amendment has been issued to include a clinical laboratory assessment on Day -2 in Part A.

Appendix 3

Additional clinical laboratory sample added to Part A. Total blood volume withdrawn in Part A updated to 124.5 mL.

Appendix 6 Study Plan (Part A)

Clinical chemistry, haematology, and urinalysis assessment added on Day -2.

Protocol Amendment 2 (Version 2.1; 29 November 2018)

This non-substantial amendment has been issued to correct minor inconsistencies in PK sampling timepoints, data cut off for dose escalation, clinical laboratory assessment timepoints, and the synopsis. Additionally, details of the injection site assessments have been added to the protocol.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Synopsis: Endpoints

Text added:

Safety:
Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, **heat pain threshold and tolerance,** and physical examinations.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from groups that received lower doses of OLP-1002.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day **10** (**216** hours postdose) from groups that received lower doses of OLP-1002.

Section 7.3.8

Entire section added to describe injection site assessments.

Appendix 3

Total blood volume for PK analysis (76 mL) added.

Appendix 6 - Schedule of assessments Part A

24 hour postdose continuous ECG recording timepoint added.

Appendix 6 - Schedule of assessments Part B

Clinical chemistry, haematology, and urinalysis for Days 1-15 previously read:

Days 2, ~~4~~, ~~7~~, ~~10~~,~~13~~

Clinical chemistry, haematology, and urinalysis for Days 1-15 now reads:

Days 2**, 5, 9, 12, 17**

PK blood sampling for Days 1-15 previously read:

Day 1 and Day ~~15~~: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, ~~8,~~ ~~11, 15~~ Predose

PK blood sampling for Days 1-15 now reads:

Day 1 and Day **13**: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, **7, 10** Predose
Day 15

Protocol Amendment 1 (Version 2; 02 October 2018)

This amendment has been generated following the non-acceptance of the original protocol (version 1) by the Medicines and Healthcare products Regulatory Agency (MHRA) on 20 September 2018. All changes made have been in response to comments provided by the MHRA.

The primary changes in this amendment are:

1. Inclusion of PK sampling in Parts A and B:
    - PK objective and exploratory endpoints added (Section 2).
    - Discussion of PK included Section 3.4.
    - PK stopping criteria added to Section 3.7.

- PK assessments included in Section 7.1.
- PK population and analysis (Section 8.2.1).
- Blood volumes updated to include samples for PK assessments (Appendix 3).

2. Exclusion and stopping criteria updated
    - Women who are pregnant or breastfeeding have been excluded from the study (Section 4.2).
    - Liver function tests, tachycardia, and hypertension stopping criteria have been updated (Section 3.7 and Section 4.4).
    - Stopping criteria for SAEs and serious AEs have been added (Section 3.7 and Section 4.4).
3. Safety, tolerability, and PK data up to Day 22 in Part B will be reviewed prior to dose escalation (Section 3.1.2).
4. Sentinel dosing included in Part B (Section 3.1.2).
5. It has been specified that the maximum dose for additional groups will not exceed 20 µg (Section 3.5.3).

Minor changes:

1. Additional clinical laboratory evaluations have been included on Day 14 in Part A.
2. The definition of the Safety population has been updated to include all subjects who receive OLP-1002.
3. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Section 1.6

Previously read:

This information, together with the pharmacodynamic (PD data, will help establish the doses and dosing regimen suitable for future studies in patients.

Now reads:

This information, together with the pharmacodynamic (PD) **and pharmacokinetic (PK)** data, will help establish the doses and dosing regimen suitable for future studies in patients.

Section 2.1

Objective added:

Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

Section 2.2.1

Endpoint added:

- **demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.**

Section 2.2.2

Endpoints added:

- **For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])**
  - **AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)**
  - **maximum observed plasma concentration (C_{max}) (actual and DN)**

  Secondary PK

  - **time of the maximum observed plasma concentration (t_{max})**
  - **apparent plasma terminal elimination half-life ($t_{1/2}$)**

- **For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)**
  - **$AUC_{0-\infty}$ (actual and DN)**
  - **C_{max} (actual and DN)**

  Secondary PK

  - **minimum observed plasma concentration (C_{min})**
  - **t_{max}**
  - **$t_{1/2}$**
  - **observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)**
  - **observed accumulation ratio based on C_{max} (RAC_{max}).**
  - **Temporal change parameter (TCP)**

Other PK parameters may also be added if deemed necessary.

Section 3.1.1

Previously read:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from the lower dose levels.

Now reads:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, **PK,** and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day **10** (**216** hours postdose) from the lower dose levels. **For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.**

Figure 1 – footnote

Text added:

Groups A9 to A11 may be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Figure 2 – footnote

Text added:

Groups B4 to B6 will be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Section 3.1.2

Previously read:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. ~~There will be no sentinel dosing in Part B.~~ For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from the lower dose levels. Part B may start after a review of the safety ~~and~~ tolerability for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Now reads:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to

be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from the lower dose levels. Part B may start after a review of the safety**,** tolerability**, and available PK data** for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Section 3.3

Previously read:

Following review of the safety, tolerability, and PD data, additional dose groups may be added to the study.

Now reads:

Following review of the safety, tolerability, **PK,** and PD data **(where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7])**, additional dose groups may be added to the study. **The maximum dose for any additional group will not exceed 20 µg.**

Section 3.4

Previously read:

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

~~Pharmacokinetic analysis will not be conducted in this study. T~~he bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose~~s~~ would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. ~~Thus, the additional burden of sampling procedures would not be justified by the quality of the data which it would generate.~~

Now reads:

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. **Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable.** It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. **In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.**

Section 3.4.1

Previously read:

In Part B, ~~all subjects in a group will be dosed on the same day~~. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3).

Now reads:

In Part B, **sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day**. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into

account when determining the doses for Part B (see Section 3.5.3). **If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.**

Section 3.5.3

Text added:

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of ~~5~~ subjects, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002. **For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.**

In Part B, doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may

be lower than the starting dose. **Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.**

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of **3 or 4** subjects**, respectively**, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Section 3.7

Previously read:

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in ~~liver function tests (~~aspartate aminotransferase, alanine aminotransferase~~,~~ alkaline phosphatase ~~and total bilirubin)~~ defined as 3 times the upper limit of normal in ~~3~~ or more subjects in a group ~~(~~confirmed with repeat testing~~)~~.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.

Now reads:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.

- **One or more subjects experience an SAE that is considered to be related to OLP-1002.**
- **Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.**
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase **or** alkaline phosphatase **(**defined as 3 times the upper limit of normal**), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be** confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- **The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).**

Section 4.2

Exclusion criteria added:

4. Female subjects who are pregnant or breastfeeding.

Section 4.4

Previously read:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal

Now reads:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal**, including:**
    - **a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),**
    - **severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),**
    - **elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),**
    - **QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),**
    - **Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),**
    - **Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).**

Section 7.1

Section added:

7.1 Pharmacokinetic Assessments

7.1.1 Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, only samples collected from subjects that received >12 µg OLP-1002 will be initially analyzed. If PK data is quantifiable at concentrations of OLP-1002 >12 µg, samples from lower dose groups will be retrospectively analyzed. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2 Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

Section 8.2

Previously read:

8.2.~~1~~ Pharmacodynamic population

The PD population will include all subjects who received at least 1 dose of ~~study treatment~~ OLP-1002 or placebo and for whom PD can be evaluated.

8.2.~~2~~ Safety Population
The safety population will include all subjects who received at least 1 dose of ~~study treatment~~ or placebo ~~and have at least 1 postdose safety assessment~~.

Now reads:

8.2.1 Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.**2** Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.**3** Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3 Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma and urine concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

Appendix 3

Table updated:

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis*	**4**	**19**	**76**
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			~~33.5~~**109.5**

Part B

	Volume per blood sample (mL)	**Maximum number of blood samples**	**Total amount of blood (mL)**
Pharmacokinetic analysis	**4**	**29**	**116**
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			~~78.5~~**194.5**

Appendix 6

PK and Blood sampling rows added to the schedule of events for Part A and Part B. In the Schedule of events for Part A, footnote e was added. In the Schedule of events for Part B, footnote b was added.

Clinical chemistry, hematology, and urinalysis was added to the Schedule of events for Part A on Day 14.

Protocol

OLP-1002 – A First-in-human, Double-blind, Placebo-controlled, Single and Multiple Subcutaneous Dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Male and Female Subjects

Protocol Status: Final
Protocol Date: 26 March 2019
Protocol Version: 4

Investigational Product: OLP-1002

Protocol Reference Number: OLP-1002-001
Covance Study Number: 8379789
EudraCT Number: 2018-003085-13

Sponsor:
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Sponsor Signatory:
[redacted]

Principal Investigator:
[redacted]

SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

March 28, 2019
Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

[redacted]

26 MAR 2019

[redacted]

Date

Principal Investigator

STUDY IDENTIFICATION

Sponsor	OliPass Corporation Ace Dongbaek Tower 20th Floor 16 Beon-gil, 16-4 Dongbaek Jungang-ro Giheung, Yongin, Gyeonggi 17015 Republic of Korea
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Study Site	Covance Clinical Research Unit Ltd. Springfield House, Hyde Street, Leeds, LS2 9LH United Kingdom
Principal Investigator	[redacted] Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH United Kingdom [redacted]
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	United Kingdom [redacted]
Clinical Laboratory	[redacted]
Statistician	[redacted] Covance

SYNOPSIS

Title of study: OLP-1002 – A first-in-human, double-blind, placebo-controlled, single and multiple subcutaneous dose, safety, tolerability, pharmacokinetic, and pharmacodynamic study in healthy male and female subjects
Objectives: The primary objective of the study is to assess the safety and tolerability of single and multiple subcutaneous doses of OLP-1002 in healthy subjects. The exploratory objectives of the study are to evaluate the pharmacodynamic effect of OLP-1002 following single subcutaneous doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of a single subcutaneous doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.
Study design: This will be a double-blind, randomized, placebo-controlled, single and multiple subcutaneous dose study conducted in 2 parts, including healthy male and female subjects.
Number of subjects: Part A: 44 subjects will be studied in 8 groups (5 groups of 4 and 3 groups of 8). Part B: 24 subjects will be studied in 3 groups (Groups B1 to B3). Up to 24 additional subjects may be recruited into Part A and Part B of the study if required.
Diagnosis and main criteria for inclusion: Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 28.0 kg/m^2 (inclusive).
Investigational products, dose, and mode of administration: Test product: OLP-1002 Proposed dose levels for Part A: 30 ng, 120 ng, 400 ng, 1.2 µg, 3 µg, 6 µg, 12 µg, and 20 µg. Proposed dose levels for Part B: the doses for Part B will be decided in consultation with the Sponsor and on the basis of data from Part A of the study. The highest dose in Part B will be up to 50% of the highest dose in Part A. Administration route: subcutaneous
Reference product and mode of administration: Reference product: placebo Administration route: subcutaneous
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to Follow-up): approximately 8 weeks for Part A and approximately 12 weeks for Part B.

Endpoints:

Pharmacodynamics:

In Part A, the analgesic effect of OLP-1002 will be investigated in 3 groups consisting of 8 subjects (6 active: 2 placebo) using experimental capsaicin-evoked pain methods. Measurement of capsaicin-evoked pain will be performed at pre-screening, baseline and on Day 2, and secondary hyperalgesia at 5 and 30 minutes post-capsaicin injection. Continuous electrocardiogram (ECG) recording will be conducted to investigate the effect of OLP-1002 on cardiac function.

Safety:

Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, heat pain threshold and tolerance, and physical examinations.

Pharmacokinetics:

In Part A, the following PK parameters will be determined where possible: area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$), maximum observed plasma concentration (C_{max}), time of the maximum observed plasma concentration (t_{max}), and apparent plasma terminal elimination half-life ($t_{1/2}$). PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

In Part B, the following PK parameters will be determined where possible: AUC over a dosing interval ($AUC_{0-\tau}$), $AUC_{0-\infty}$, $C_{max,}$ minimum observed plasma concentration (C_{min}), t_{max}, $t_{1/2}$, observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$), observed accumulation ratio based on C_{max} (RAC_{max}), and Temporal change parameter (TCP). PK samples from all groups in Part B will be analyzed.

Statistical methods:

Pharmacodynamics:

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of pharmacodynamic data is planned.

Safety:

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

Pharmacokinetics:

Individual plasma concentrations and PK parameters of OLP-1002 will be listed and summarized using descriptive statistics. Individual and mean OLP-1002 concentration-time profiles will be presented graphically.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours postdose
BMI	body mass index
C_{max}	maximum observed plasma concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSA	clinical study agreement
DN	Dose normalized
DRG	dorsal root ganglion
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
E_{max}	maximum pain intensity
FCA	Freund's Complete Adjuvant
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SC	subcutaneous(ly)
SNL	spinal nerve ligation
$t_{1/2}$	elimination half-life
tE_{max}	time of maximum pain intensity
T_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
VAS	Visual Analogic Scale
VGSC	voltage-gated sodium channel

1. INTRODUCTION

1.1. Overview

OLP-1002 is a novel peptide nucleic acid (PNA) derivative which acts as a specific voltage-gated sodium channel (VGSC) protein ($Na_v1.7$) inhibitor, and is being developed by OliPass for the treatment of pain.

The $Na_v1.7$ protein is a subtype of VGSCs. $Na_v1.7$ is particularly important in nociception and pain signaling, with congenital loss-of-function mutations in $Na_v1.7$ resulting in the inability to experience pain. Selective $Na_v1.7$ inhibitors are believed to have the potential to treat severe pain safely[1]. The active sites of VGSC subtypes are virtually indistinguishable by their 3-dimensional structure and thus the discovery of selective $Na_v1.7$ small molecule inhibitors has been extremely challenging. Since inhibition of $Na_v1.5$ subtype elicits long QT cardiotoxicity, inhibition of $Na_v1.5$ subtype should be avoided at therapeutic doses.

To date, there are several $Na_v1.7$ inhibitors claimed to be selective that have been evaluated in human subjects:

- Vixotrigine (formerly known as raxatrigine) inhibits $Na_v1.7$ as well as other VGSC subtypes. Vixotrigine is in phase III clinical development for trigeminal neuralgia. Due to the limited $Na_v1.7$ selectivity over $Na_v1.5$, vixotrigine was evaluated primarily in patients with a low heart risk.
- Funapide is a $Na_v1.7$ inhibitor with limited $Na_v1.7$ selectivity, and was in phase IIb clinical trials as of July 2014. Although funapide showed analgesic activity in a small number of erythromelalgia patients, dose-limiting adverse events (AEs), including dizziness and somnolence, were observed[2]. The central nervous system (CNS) AEs were due to its poor $Na_v1.7$ selectivity.
- PF-05089771 is a $Na_v1.7$ selective inhibitor with a claimed $Na_v1.7$ selectivity of > 2000-fold versus other subtypes of sodium channel and was evaluated in patients of erythromelalgia or dental pain. It is thought low drug concentrations achieved in the target tissue could be a possible explanation for its poor analgesic activity in human patients[3].

OLP-1002 is fully complementary to a 14-mer RNA sequence spanning the junction of intron 4 and exon 5 in the human SCN9A pre-mRNA which codes for the $Na_v1.7$ channel. OLP-1002 yields SCN9A mRNA splice variant(s) encoding variant $Na_v1.7$ protein(s) lacking the sodium channel activity (ie, a non-functional channel), thereby inhibiting $Na_v1.7$ channel function.

1.2. Summary of Nonclinical Pharmacology

1.2.1. In Vitro Pharmacology Studies

Overall, results from the in vitro pharmacology studies showed OLP-1002 elicits responses consistent with its designed function[4]. It inhibits SCN9A mRNA expression and yields the

$Na_v1.7$ variant protein or proteins lacking sodium channel activity. Its effects are highly selective, which may provide for an improved margin of safety compared to other $Na_v1.7$ inhibitors.

OLP-1002 at 1 to 100 zM in PC3 prostate carcinoma cells induced exon skipping and yielded SCN9A mRNA splice variant(s) encoding a $Na_v1.7$ variant protein or proteins lacking sodium channel activity.

In rat dorsal root ganglion (DRG) neuronal cells, OLP-1002 at 1000 zM inhibited $Na_v1.7$ protein expression by > 50%, while OLP-1002R at 100 and 1000 zM inhibited $Na_v1.7$ expression almost completely. As OLP-1002R is fully complementary to rat SCN9A pre-mRNA, OLP-1002R would be predicted to be more potent than OLP-1002 in this cell type.

SCN9A mRNA expression level was evaluated by quantitative polymerase chain reaction (qPCR). OLP-1002 inhibited the expression of the SCN9A mRNA in PC3 cells with sub-attomolar potency.

In SH-SY5Y human neuroblastoma cells stimulated with tumor necrosis factor (TNF)-1α to upregulate the expression of SCN9A mRNA, OLP-1002 decreased expression by 46% to 49% at 1 fM to 10 pM. In rat DRG neuronal cells, OLP-1002 at 1 fM significantly decreased SCN9A mRNA expression by 54%.

In rat DRG neuronal cells, OLP-1002 markedly and significantly inhibited the sodium current by 77% at 0.1 aM and 73% at 1 aM, while for OLP-1002R, the inhibition was 66% at 0.1 aM and 70% at 1 aM. Given that rat DRG neuronal cells express various subtypes of sodium channel, the observed inhibitions of 66% to 77% correspond to the complete knockout of the $Na_v1.7$ sodium channel subtype with OLP-1002 or OLP-1002R.

The $Na_v1.7$ selectivity over $Na_v1.5$ was evaluated in H9C2 rat cardiomyocytes which are known to abundantly express the rat $Na_v1.5$ sodium channel subtype. Following incubation with OLP-1002 or OLP-1002R at 1 aM or 1 pM, there were no notable decreases in the sodium current. Considering that OLP-1002 and OLP-1002R inhibit the expression of $Na_v1.7$ protein at 1 aM or lower in rat DRG neuronal cells, the $Na_v1.7$ selectivity of OLP-1002 and OLP-1002R over $Na_v1.5$ is estimated to be in excess of one million-fold. Such a large $Na_v1.7$ selectivity over $Na_v1.5$ has not been realized with small molecule $Na_v1.7$ inhibitors, suggesting that OLP-1002 potentially offers pain management with much greater cardiovascular safety.

1.2.2. In Vivo Pharmacology Studies

Spinal nerve ligation (SNL) has been widely applied as a rat model for neuropathic pain. OLP-1002 and OLP-1002R were found to be very potent, but highly variable in potency, in reversing neuropathic allodynia in this model. Analyses of the therapeutic potency strongly suggested that a marked proportion of subcutaneously (SC) administered OLP-1002 or OLP-1002R may have been topically delivered directly to the spinal nerves exposed in the dorsal cavity created during the SNL modelling. In addition, the variability of the therapeutic potency may be due to a variable degree of healing of the SNL surgery wound. If an animal

recovers slowly, the animal tends to be left with a dorsal cavity. Therefore, estimations of potency in these studies with this model should be treated with caution.

In one study using the SNL model, allodynia in rats was slowly and gradually reversed by OLP-1002 SC administered at nominal doses of 1, 3, and 6 pmol/kg once every 2 days (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). As the onset time for pain reduction was 4 days, the doses used were not sufficient for fast onset of activity. In this study, the animals should have reasonably recovered from the dorsal wound, and therefore less susceptible to topical delivery directly to the exposed spinal nerves. However, in another study in this model, when OLP-1002 was intraperitoneally (IP) administered once every 3 days to avoid the likelihood of local delivery to the spinal nerves, OLP-1002 surprisingly reversed the allodynia at 5 fmol/kg, and was superior or comparable to pregabalin 30 mg/kg, a gold standard for neuropathic pain studies. The high potency shown at 5 fmol/kg IP strongly suggests the possibility that OLP-1002 is efficiently absorbed by the enteric nervous system, travels to the spinal cord, and then redistributes to the spinal nerves of the SNL ligation. This opens the possibility of efficient oral delivery of OLP-1002 to the spinal cord.

When evaluated for their ability to reverse the inflammatory pain in rats inflicted with Freund's Complete Adjuvant (FCA)-induced severe paw inflammation, OLP-1002 at 300 pmol/kg and OLP-1002R at 100 pmol/kg significantly reversed the thermal hyperalgesia, and both were more effective than pregabalin 30 mg/kg.

Paw burn injury induces hyperalgesia in rats and is known to upregulate $Na_v1.7$ expression in the L5 and L6 DRGs of the affected side. Burn injury induces a far weaker degree of paw inflammation than FCA-induced paw inflammation. OLP-1002 SC administered inhibited the thermal hyperalgesia in paw burn injury in a dose-dependent manner. At 25 fmol/kg, OLP-1002 did not inhibit thermal hyperalgesia. Although OLP-1002 at 625 fmol/kg significantly inhibited the thermal hyperalgesia, the efficacy was moderate and weaker than pregabalin 30 mg/kg. This suggests that SC dosing does not offer the local topical delivery to spinal nerves in this model as seen in rats without a dorsal cavity wound. In this study, the $Na_v1.7$ expression in the DRG of the burn injury side significantly decreased by 58% with 625 fmol/kg OLP-1002, validating the target engagement for analgesic activity.

An intraplantar injection of formalin induces severe acute pain. The contributors to acute pain are known to be complex and require further elucidation. However, acute peripheral inflammation is known to contribute much to Phase II Pain (pain from 10 to 40 min after the formalin injection). In this model, OLP-1002 significantly inhibited Phase II Pain at comparable or saturated efficacy when SC administered at 10 to 100 pmol/kg (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). Thus peripheral acute inflammatory pain could be treated with 10 pmol/kg or less.

1.2.3. Ex Vivo Pharmacology Studies

One day post-SC injection, OLP-1002 and OLP-1002R at 100 pmol/kg significantly inhibited the expression of $Na_v1.7$ protein by 39% and 57%, respectively, in the spinal cord of rats subjected to SNL.

In other rats subjected to SNL, OLP-1002R slowly and gradually reversed the allodynia in a dose-dependent manner. OLP-1002R at 30 fmol/kg (the highest dose administered) had the greatest effect, but the dose was not high enough to elicit full therapeutic efficacy. OLP-1002R inhibited expression of $Na_v1.7$ protein in these animals, most notably at 1 fmol/kg, and decreased SCN9A mRNA expression by approximately 40% at 1 to 30 fmol/kg. The observed inhibitions were largely consistent with the in vivo therapeutic activity findings.

Taking all the in vivo and ex vivo findings together, OLP-1002R was concluded to inhibit neuropathic allodynia by inhibiting the expression of the SCN9A mRNA and the $Na_v1.7$ protein.

1.3. Summary of Safety Pharmacology

In vitro, OLP-1002 did not inhibit the human ether-à-go-go-related gene (hERG) channel current expressed in human embryonic kidney (HEK) cells at the highest concentration tested 2 μM (the limit of the validated analytical method for OLP-1002).

In the in vivo safety pharmacology studies, OLP-1002 SC administered at dose levels up to 100 nmol/kg had no effect on body temperature, neurological function, or respiratory function in rats, and had no significant toxic effect on cardiovascular function in cynomolgus monkeys.

1.4. Summary of Toxicology

In rats, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included pigment accumulation in the kidney of males administered 100 nmol/kg/dose and females administered ≥ 10 nmol/kg/dose, foreign material and vacuolated macrophage infiltrates in males and/or females administered ≥ 1 nmol/kg/dose, and an increased incidence and/or severity of mononuclear cell infiltrates at the injection sites in males and/or females administered ≥ 10 nmol/kg/dose. These findings persisted through the recovery phase in animals administered 100 nmol/kg/dose. However, the effects were considered non-adverse due to their mild severity and lack of impact on animal health and wellbeing. The no-observed-adverse-effect level (NOAEL) was 100 nmol/kg/dose. This dose level corresponded to maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from 0 to 24 hours postdose (AUC_{0-24}) values of 27.6 ng/mL and 174 ng·hr/mL, respectively, in males and 24.9 ng/mL and 128 ng·hr/mL, respectively, in females on Day 88 of the dosing phase.

In cynomolgus monkeys, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included mononuclear cell infiltrates at the SC injection sites of animals administered ≥ 10 nmol/kg/dose. This finding was not resolved with the completion of the recovery phase. However, the effects of 100 nmol/kg/dose were considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing. The NOAEL was 100 nmol/kg/dose (equivalent to 462.29 μg/kg/dose), which corresponded to C_{max} and AUC from 0 to 72 hours postdose (AUC_{0-72}) values of 121 ng/mL and 2840 ng·hr/mL in males, respectively, and 216 ng/mL and 4840 ng·hr/mL in females, respectively, on Day 88 of the dosing phase.

The genotoxic and mutagenic potential of OLP-1002 was evaluated with standard Good Laboratory Practice (GLP) via in vitro bacterial mutagenicity and chromosomal aberration studies, and was found to be negative.

1.5. Summary of Nonclinical Pharmacokinetics

In rats, following a single SC dose of ^{14}C-OLP-1002, the time of maximum observed concentration (T_{max}) was 0.5 to 1 hour for both radioactivity and parent compound. Plasma concentrations of total radioactivity were quantifiable through the last sampling time of 72 hours postdose, but was variable for the parent compound. The elimination half-life ($t_{1/2}$) of total radioactivity from plasma was 23 hours. Total radioactivity distributed into tissues, including those of the CNS protected by the blood-brain barrier. ^{14}C-OLP-1002-derived total radioactivity was not rapidly excreted from rats, with minimal amounts present in urine and feces. The bulk of the total radioactivity remained in carcasses, primarily in kidneys (cortex and medulla) and liver. Parent ^{14}C-OLP-1002 was present in plasma and tissues, but concentrations declined over time and were substantially lower than total radioactivity concentrations at the later sampling times.

After a single SC administration of ^{14}C-OLP-1002 to rats, the highest concentrations of total radioactivity were retained predominantly in the liver (10.4% to 13.3% of the dose), kidney cortex (3.47% to 4.96%), and kidney medulla (1.10% to 1.59% of the dose) through 168 hours postdose. For all other tissues, the total amounts of total radioactivity were substantially less, ranging from 0.0000203% in the 5th DRG to 0.327% in the spleen. Radioactivity was excreted slowly via both the renal and fecal routes of elimination. Total average recoveries of radioactivity in urine and feces through 336 hours postdose accounted for 2.31% and 1.75% of the administered radioactivity, respectively. The bulk of the administered total radioactivity was retained in the rat carcasses through 168, 336, 504, and 840 hours postdose. The kidney cortex, kidney medulla, and liver were the 3 tissues that retained the greatest amounts of the administered radioactivity.

Following a 16.1-µg/kg dose in rats, the plasma concentrations were still quantifiable at 72 hours postdose and the rate of elimination was slow, with $t_{1/2}$ 17.5 hours. It was not possible to accurately define the elimination phase for the 2.67- and 5.28-µg/kg dose levels.

In cynomolgus monkeys, following a single SC dose of ^{14}C-OLP-1002, T_{max} ranged from 0.25 to 1 hour for both total radioactivity and parent compound. Concentrations of total radioactivity were sustained in blood and plasma through the last sampling time of 144 hours postdose. Concentrations of parent compound were sustained in plasma through the last sampling time of 144 hours postdose in 2 of 3 monkeys, and were similar to plasma total radioactivity concentrations at 8 hours postdose. From 24 to 144 hours postdose, plasma concentrations of total radioactivity were substantially higher than for parent ^{14}C-OLP-1002 plasma concentrations.

The mean C_{max} of parent ^{14}C-OLP-1002 in plasma was 1.96 ng/mL. The mean plasma T_{max} was 0.833 hours. Plasma exposure of parent ^{14}C-OLP-1002 based on AUC extrapolated to infinity ($AUC_{0-\infty}$), was 12.7 ng·h/mL. After reaching C_{max}, plasma concentrations of parent ^{14}C-OLP-1002 declined with a mean $t_{1/2}$ of 84 hours.

1.6. Study Rationale

This is the first time OLP-1002 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data when OLP-1002 is administered SC as single and multiple doses to healthy subjects. This information, together with the pharmacodynamic (PD) and pharmacokinetic (PK) data, will help establish the doses and dosing regimen suitable for future studies in patients. The analgesic effects of OLP-1002 on a capsaicin-induced pain model will also be investigated.

1.7. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. For subjects in the PD assessment groups in Part A there will be some additional discomfort from the capsaicin test. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with OLP-1002 may be found in the Investigator's Brochure[4].

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is to assess the safety and tolerability of single and multiple SC doses of OLP-1002 in healthy subjects.

The exploratory objectives of the study are to evaluate the PD effect of OLP-1002 following single SC doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of single SC doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- incidence and severity of AEs
- vital signs measurements (blood pressure, pulse rate, respiratory rate)
- 12-lead electrocardiogram (ECG) parameters
- incidence of clinical laboratory abnormalities, based on clinical chemistry, hematology, and urinalysis test results
- physical examinations
- injection site assessment.

- demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.

2.2.2. Exploratory Endpoints

The following exploratory objectives will be assessed:

- pain intensity and duration will be assessed by AUC, maximum pain intensity (E_{max}), and time of maximum pain intensity (tE_{max}), calculated using a capsaicin-evoked pain model. The exploratory endpoint of secondary hyperalgesia will be assessed by the area of secondary area of hyperalgesia (Part A only).
- continuous (24-hour) ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval (Part A).
- heat pain threshold measurements and heat pain tolerance measurements.
- For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:

  Primary PK

  - area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])
  - AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)
  - maximum observed plasma concentration (C_{max}) (actual and DN)

  Secondary PK

  - time of the maximum observed plasma concentration (t_{max})
  - apparent plasma terminal elimination half-life ($t_{1/2}$)
- For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:

  Primary PK:

  - AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)
  - $AUC_{0-\infty}$ (actual and DN)
  - C_{max} (actual and DN)

  Secondary PK

  - minimum observed plasma concentration (C_{min})
  - t_{max}
  - $t_{1/2}$
  - observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)
  - observed accumulation ratio based on C_{max} (RAC_{max}).
  - Temporal change parameter (TCP)

Other PK parameters may also be added if deemed necessary.

3. INVESTIGATIONAL PLAN

This will be a double-blind, randomized, placebo-controlled, single and multiple SC dose study conducted in 2 parts.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, PK, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

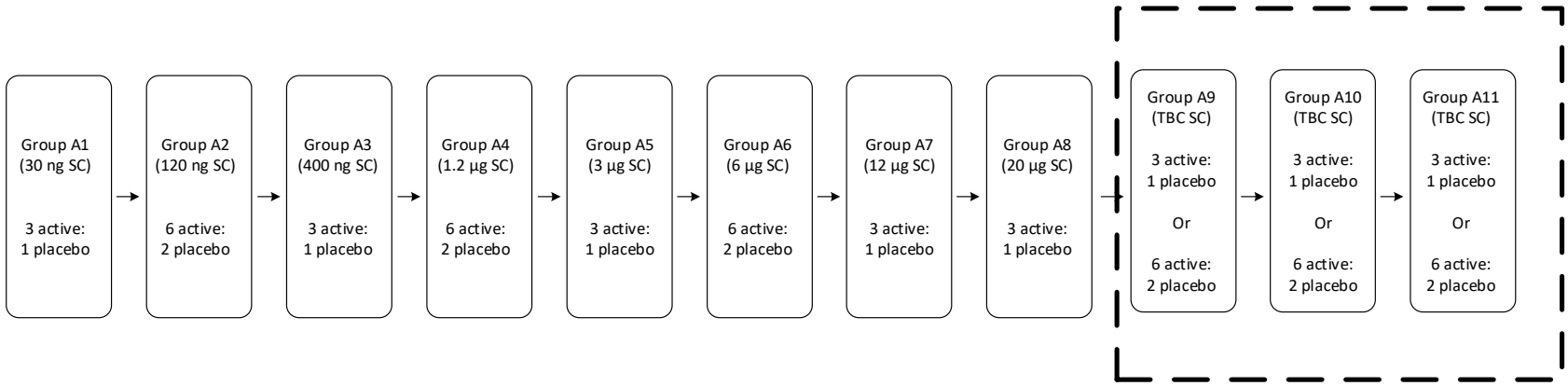
Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 10 (216 hours postdose) from the lower dose levels. For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.

In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, and A6 will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.

Sentinel dosing will be employed for all groups in Part A. To maintain the blind in a 4-subject group, the first subject will be dosed 48 hours before the second subject, and the second subject will be dosed 48 hours prior to the third and fourth subjects. In PD assessment groups, 2 subjects (1 active: 1 placebo) will be dosed 48 hours before the remaining 6 subjects (5 active: 1 placebo).

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic (Part A)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
Groups A9 to A11 may be included if required; dose levels will not exceed the maximum proposed dose of 20 µg.
Three groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

3.1.2. Part B

Part B will comprise a multiple-dose, sequential-group study. Overall, 24 subjects will be studied in 3 groups (Groups B1 to B3), with each group consisting of 8 subjects. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety and tolerability (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15.

All subjects will return for non-residential visits on Days 18 (± 2 days), 22 (± 2 days), 25 (± 2 days), and 29 (± 2 days), and for a poststudy visit on Day 57 (± 2 days).

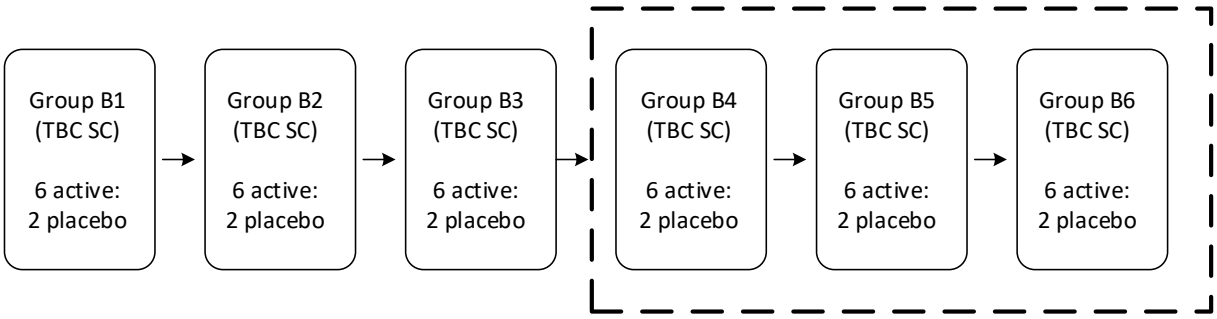
In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from the lower dose levels. Part B may start after a review of the safety, tolerability, and available PK for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

An overview of the study design is shown in Figure 2.

Figure 2: Study Schematic (Part B)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
All doses will be confirmed based on results of Part A; dose levels will not exceed the maximum proposed dose of 20 µg..
Groups B4 to B6 will be included if required.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 12 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Start of Study and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, PK, and PD data (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7]), additional dose groups may be added to the study. The maximum dose for any additional group will not exceed 20 µg. Up to 3 further groups of 8 subjects (6 active: 2 placebo) may be included in Part A, and up to 3 additional groups of 8 subjects (6 active: 2 placebo) may be included in Part B. The requirement for additional groups will be agreed with the Sponsor and documented in the Trial Master File (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential-group, ascending-dose design has been chosen for safety reasons as OLP-1002 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Subcutaneous doses have been chosen for both parts of the study, as this is the intended clinical route of administration.

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of

safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore, if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.

This study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Continuous ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing in Part A for groups consisting of 4 subjects will be such that there will be 48 hours between the first and second subjects, and 48 hours between the second and remaining 2 subjects in each group. For groups in Part A consisting of 8 subjects, 2 subjects (1 active: 1 placebo) will be dosed 48 hours prior to the remaining 6 subjects.

In Part B, sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.

In Parts A and B, there will be a minimum interval of a 10-minute gap between dosing subjects (when dosed on the same day). Continuation to dose the remaining subjects in a group will be at the Investigator's discretion.

3.4.2. Pharmacodynamic Assessment

Pharmacodynamic assessments will be conducted for subjects in Groups A2, A4, and A6.

Human experimental pain models using healthy volunteers can be used to assess the effect of a drug or treatment under controlled clinical conditions. Capsaicin is a vanilloid responsible for the pungent taste of hot peppers. In mammalian species, capsaicin-induced pain is mediated through Group C nerve fibers following activation of vanilloid 1 transient receptor potential (TRPV1) channels[5]. $Na_v1.7$ has been implicated in controlling neuropeptide release from C-fibers, and suppression of capsaicin-induced neurogenic flair has been demonstrated by an $NA_v1.7$ inhibitor[6].

Several studies have used intradermal capsaicin for human experimental pain studies[7,8]. It has been possible to demonstrate dose-dependent responses, with intradermal injections of 100 µg generally agreed to be the ideal dosage for these studies. Intradermal injection of capsaicin causes a brief stinging/burning pain at the injection site (spontaneous pain) followed by development of secondary hyperalgesia, which can be assessed using equipment such as Von Frey hairs. A study by Gazerani et al.[5] found that the response was site-specific and while peak pain intensity and duration were greatest in the forehead it was found that areas of visible flare and secondary hyperalgesia were significantly larger in the forearm, making the forearm the most suitable site for experimentation.

Covance CRU, Leeds, UK in 2009 performed a validation study using intradermal capsaicin (Covance CRU Study: 9999-004) with between-subject and within-subject variability demonstrating that the assessments can be reliably conducted to assess pharmacological response.

For these reasons, it has been decided to:

- Measure both capsaicin-evoked pain and secondary hyperalgesia.
- Limit the number of capsaicin tests to 3 for each subject (pre-screening, baseline, and 48 hours postdose)
- Exclude subjects who have pain <3 or >9 (using a Visual Analogic Scale [VAS]) at the pre-screening visit from PD assessment groups.

3.5. Selection of Doses in the Study

3.5.1. Starting Dose

The rat has been identified as the most sensitive species in a 13-week SC toxicity study with a 4-week recovery phase (Covance study no. 8355564). The NOAEL was the 100 nmol/kg/dose (462.29 µg/kg/dose). This dose level resulted in C_{max} of 27.6 ng/mL and 24.9 ng/mL in males and females, respectively, and AUC_{0-24} of 174 ng.h/mL and 128 ng.h/mL in males and females, respectively[4]. As the exposure was lower in the female rats these data have been used to calculate the safety margins.

The dose of 462.29 µg/kg/dose corresponds to human equivalent doses (HEDs) of 74.8 µg/kg/dose, which gives a maximum recommended starting dose (MRSD) of 444 µg for a 60-kg human and thus a 15000-fold safety margin to the proposed starting dose of 30 ng and 22-fold margin to the proposed maximum dose of 20 µg. Additionally the NOAEL dose in the cynomolgus monkey was identified as 100 nmol/kg/dose (462.29 µg/kg/dose), which gives a higher HED of 150 µg/kg/dose.

In vivo, doses of 10 pmol/kg/dose (0.0462µg/kg/dose) or less were found to inhibit peripheral acute inflammatory pain. The equivalent human dose for a 60-kg human is 44 ng, thus a dose at which minimal biological effect is anticipated has been selected as the starting dose of 30 ng.

3.5.2. Exposure

Human exposures have been estimated from the pharmacokinetics in the cynomolgus monkey since a non-human primate represents the most closely related species. Approximately dose-proportional exposure was seen in the 13-week toxicity study (Covance study no. 8355565) and ^{14}C pharmacokinetic study (Covance study no. 8355568) over a dose range of approximately 1.1 to 100 nmol/kg (5.06 to 462.29 µg/kg)[4]. However, the lowest dose (5.06 µg/kg) from the ^{14}C study has been used to estimate the human exposures as it is closest to the proposed human dose range and has the sufficient quantifiable data.

The assumptions made in the human exposure estimation were that human exposure would be similar to the cynomolgus monkey and that exposure would be linear with dose. Following a dose of 5.06 µg/kg in the cynomolgus monkey, the C_{max} was 1.96 ng/mL and $AUC_{0-\infty}$ was 12.7 ng.h/mL. The extrapolated exposures at the planned human doses are shown in Table 1 with margins calculated to the exposures at the NOAEL in the female rat.

Table 1: Estimated Human Exposure and Safety Margins to the NOAEL in the Female Rat for Single Dose Administration of OLP-1002

Human dose		Single dose to human		Safety margins for single dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\infty}$
0.03	0.000500	0.000194	0.00125	129000	102000
0.12	0.00200	0.000775	0.00502	32100	25500
0.4	0.00667	0.00258	0.0167	9640	7650
1.2	0.0200	0.0077	0.0502	3210	2550
3	0.0500	0.0194	0.125	1290	1020
6	0.100	0.0387	0.251	643	510
12	0.200	0.0775	0.502	321	255
20	0.333	0.129	0.837	193	153

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

The dosing interval currently anticipated for the multiple-ascending-dose part of this study is 72 hours or 96 hours. Thus the average dosing interval (82 hours) is similar to the half-life determined in the monkey ^{14}C study of 84 hours. Dosing at approximately once per half-life would be anticipated to result in accumulation of around 2-fold. However, higher levels of accumulation were observed (2.28-fold for C_{max} and 3.76-fold for AUC_{0-24}) on Day 88 at the top dose group (100 nmol/kg, 462.28 µg/kg) in the 13-week cynomologus monkey toxicity study following twice-weekly dosing (every 72 or 96 hours). Calculations were performed to estimate the likely human half-life using a standard 1-point allometric approach from the ^{14}C cynomolgus monkey pharmacokinetic study data. The exponents used were 0.75 for apparent total plasma clearance (CL/F) and 1 for apparent volume of distribution (V_z/F) values combined with the average body weight of the animal (3.1 kg) and scaling to a 60 kg human [9–11]. This resulted in a human half-life estimate of 180 h which in turn gave an accumulation estimate of 3.7-fold based upon a dosing interval of 82 h. This further supports the use of the greater than 2-fold accumulation from the 13-week cynomolgus study to estimate exposure following multiple dosing. Multiplication of the exposure estimates for the single ascending

dose by 2.28 for C_{max} and 3.76 for AUC resulted in exposure estimates for multiple dosing presented in Table 2.

Table 2: Estimated Human Exposure and Safety Margin to the NOAEL in the Female Rat for Multiple Dose Administration of OLP-1002

Human dose		Multiple dose to human		Safety margins for multiple dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\tau,ss}$
0.03	0.000500	0.000442	0.00472	56000	27000
0.12	0.00200	0.00177	0.0189	14100	6800
0.4	0.00667	0.00589	0.0629	4230	2030
1.2	0.0200	0.017663	0.189	1410	680
3	0.0500	0.0442	0.472	560	270
6	0.100	0.0883	0.944	282	136
12	0.200	0.177	1.89	141	68
20	0.333	0.294	3.15	85	41
30	0.500	0.442	4.72	56	27

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

3.5.3. Proposed Doses

The proposed IMP dose levels for Parts A and B are shown in Table 3.

Table 3: Proposed Investigational Medicinal Product Dose Levels for Parts A and B

Study Part	Group	Dose (OLP-1002)
Part A	A1	30 ng or placebo
	A2	120 ng or placebo
	A3	400 ng or placebo
	A4	1.2 µg or placebo
	A5	3 µg or placebo
	A6	6 µg or placebo
	A7	12 µg or placebo
	A8	20 µg or placebo
	A9*	TBC or placebo
	A10*	TBC or placebo
	A11*	TBC or placebo
Part B	B1	TBC or placebo
	B2	TBC or placebo
	B3	TBC or placebo
	B4*	TBC or placebo
	B5*	TBC or placebo
	B6*	TBC or placebo

Abbreviations: TBC = to be confirmed
* groups to be included if required.

In Parts A and B, there should not be an increase of > 3-fold between dose levels above 120 ng.

For Part B, dose levels, dosing frequency, and dosing duration will be decided, in consultation with the Sponsor, on the basis of data from Part A of the study. Since predictions of human exposure of OLP-1002 suggest that OLP-1002 concentrations may be not be quantifiable and human data have been estimated from a single species, it is proposed that the highest dose in the multiple-ascending-dose part will be up to 50% of the highest dose in the single-ascending-dose part (ie, if the highest dose in the single-ascending-dose part is 20 µg, the highest dose in the multiple-ascending-dose part will be 10 µg). Therefore, if the predicted accumulation of 3.7-fold occurs, the highest exposure in the multiple-ascending-dose part will not exceed ~2-fold the maximum exposure in the single-ascending-dose part.

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

3.6. Dose Escalation

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 10 (216 hours postdose) from groups that received lower doses of OLP-1002. For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of 3 or 4 subjects, respectively, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

The justification for this is as follows:

- The study drug is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.

- A minimum of 3 subjects receiving the active drug is considered sufficient to characterize the safety profile for OLP-1002.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarizing results from all available safety assessments, will be sent to the Sponsor and a dose-escalation meeting will occur prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PD data may also be reviewed on an ongoing basis. In the event of a disagreement between Sponsor and Investigator on the dose-escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- One or more subjects experience an SAE that is considered to be related to OLP-1002.
- Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase (defined as 3 times the upper limit of normal), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).

If the sponsor deems it appropriate to resume dosing after the internal safety review, it can be done after the approval of a substantial protocol amendment.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Healthy male or females of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) between 18.0 and 28.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, single 12-lead ECG (resting heart rate > 45 bpm and < 90 bpm), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening as assessed by the Investigator (or designee).
4. Willing to abide by the contraception requirements as detailed in Appendix 4.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Any of the following:
    - QTcF > 450 ms confirmed by repeat measurement.
    - QRS duration > 110 ms confirmed by repeat measurement.
    - PR interval > 220 ms confirmed by repeat measurement.
    - findings which would make QTc measurements difficult or QTc data uninterpretable.
    - history of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
4. Female subjects who are pregnant or breastfeeding.
5. History of alcoholism or drug/chemical abuse within 1 year prior to Screening.

6. Alcohol consumption of > 21 units per week for males and >14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
7. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
8. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2).
9. Active skin conditions such as dermatitis, allergy, eczema, psoriasis, or abnormal healing.
10. Tattoos, scars, or moles that in the opinion of the Investigator are likely to interfere with dosing or study assessments at any of the potential injection sites.
11. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days or 5 half-lives of the investigational product, whichever is longer, prior to Check-in.
12. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
13. Use or intend to use any prescription medications/products other than hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptive concomitant medications within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
15. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and/or Sponsor have given their prior consent.
16. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in.
17. Receipt of blood products within 60 days prior to Check-in.
18. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
19. Poor peripheral venous access.
20. Have previously completed or withdrawn from this study or any other study investigating OLP-1002, and have previously received the investigational product.
21. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
22. Part A – PD assessment groups only
    - Subjects considered non-acceptable responders to the intradermal capsaicin test at screening, defined as maximum VAS score of < 3.0 or > 9.0.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number at the time of their randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A, Subjects 101, 102, etc., in Part B Subjects 201, 202, etc.). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal, including:
    - a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),
    - severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),
    - elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),
    - QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),
    - Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),
    - Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Vials of OLP-1002 Injection Solution 100 µg/mL (1.5 mL in 5-mL vials) and the Diluent for OLP-1002 Injection Solution (5 mL in 10-mL vials) will be supplied by the Sponsor, along with the batch/lot number and Certificate of Analysis. The Diluent for OLP-1002 Injection Solution will also be used as the Placebo formulation. A certificate of batch certification and release, authorized by a Qualified Person in the European Union (EU) will also be issued, by a Covance CRU Qualified Person, for each batch of IMP imported into the EU.

The IMPs will be stored according to the instructions on the label at the CRU in a location that is locked with restricted access.

Dose solutions (OLP-1002 Injection Solution diluted with the Diluent for OLP-1002 Injection Solution) will be prepared by Covance CRU Pharmacy staff in accordance with instructions provided in the Pharmacy Manual. The Placebo formulation will be the Diluent for OLP-1002 Injection Solution without further manipulation.

5.2. Study Treatment Administration

Subjects will be administered the IMP in numerical order. OLP-1002 will be administered by SC injection in the upper arm. If subcutaneous dosing of OLP-1002 in the upper arm is not possible, the subject may be dosed in the abdomen at the Investigator's discretion. For subjects in Groups A2, A4, and A6, dosing will be on the opposite arm to the intradermal capsaicin test.

5.3. Randomization

The randomization code will be produced by the statistics department at Covance using a computer-generated pseudo-random permutation procedure. In Part A, 1 subject in groups

consisting of 4 subjects, and 2 subjects in groups consisting of 8 subjects, will be randomly assigned to receive placebo. In Part B, 2 subjects per group will be randomly assigned to receive placebo. All other subjects in a group will be randomized to receive OLP-1002.

Prior to the start of the study, a copy of the master randomization code will be supplied into the Covance CRU pharmacy staff (in sealed envelopes).

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo solution will be identical in appearance to the OLP-1002.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

To maintain the blind, the Investigator will be provided with sealed randomization code-break envelopes for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose-escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

All doses of IMP will be administered by suitably qualified study site staff.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription medications/products from 14 days prior to dosing until the Follow-up visit, and non-prescription medications/products from 7 days prior to dosing until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests. On dosing days, subjects will receive a light breakfast approximately 2 hours prior to dosing. Meals will be provided as appropriate at other times and water will be freely available at all times.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until the Follow-up visit.

Xanthine-containing foods and beverages will not be allowed from 36 hours before Check-in until Discharge from the site. Xanthine-containing foods and beverages will also not be allowed form 36 hours before non-residential site visits.

Chili pepper/hot sauce will not be allowed for 48 hours prior to Check-in for all subjects. Subjects in Groups A2, A4, and A6 will not be allowed chili pepper/hot sauce for 48 hours prior to their pre-screening visit.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until Discharge. Following discharge, up to 2 units/day of alcohol are permitted until 36 hours before each non-residential visit and the Follow-up visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 3 days before Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during this

time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit. Subjects should not be in receipt of blood products for 60 days prior to check-in.

6.6. Other Restrictions

Subjects in Groups A2, A4, and A6 will not be allowed to shower within 1 hour prior to the capsaicin-evoked pain tests at prescreening, predose, and postdose.

Subjects will not be allowed to apply moisturizing creams or oils to the dosing site within 1 hour prior to dosing, or to the assessment site within 1 hour prior to the capsaicin-evoked pain test.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- vital signs
- blood samples
- cardiac monitoring/ECG extractions
- any other procedures.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, PK analysis will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the

event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Pharmacodynamic Assessments

Capsaicin intradermal test will be performed for subjects in Groups A2, A4, and A6. Each subject will be tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).

7.2.1. Capsaicin-evoked Pain Model

The capsaicin model will be conducted by intradermal injection of capsaicin (100 µg in 100 µL of sterile saline containing 8% [w/w] Tween 80) into the skin of the anterior aspect of the forearm, midway between the elbow and the wrist. The bleb area (wheal) will be a sign of local plasma extravasation. An assessment of the pain intensity related to capsaicin injection will be estimated by repeated use of a VAS from injection to 5 minutes post-injection or until the pain intensity returned to zero. The AUC, E_{max}, and tE_{max} will be calculated and reported using dedicated software.

7.2.2. Secondary Hyperalgesia

The area of secondary hyperalgesia will be quantified with a 60-g weighted von Frey hair, by stimulating along 8 linear paths (4 vectors crossing at the location of the injection site) arranged vertically and horizontally around the stimulation site in 5-mm steps (starting approximately 6 cm away from the injection site). The area of secondary hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection.

7.3. Safety and Tolerability Assessments

Safety and tolerability assessments will be conducted at the times indicated in the Schedule of Assessments (Appendix 6). Timepoints may be adjusted based on an ongoing review of the data, and additional assessments may be conducted if deemed necessary by the Investigator or designee.

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked

about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a follicle-stimulating hormone (FSH) test and pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

Subjects must be supine for at least 5 minutes before blood pressure, pulse rate, and respiratory rate measurements.

7.3.4. Electrocardiogram

7.3.4.1. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value > 500 msec
- QTcF change from the mean baseline (Day 1 predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.4.2. Continuous (24-hour) Electrocardiogram

At the times indicated in the Schedule of Assessments (Appendix 6), continuous (24-hour) ECGs will be performed.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint. Each extraction will last for 5 minutes. Environmental distractions (eg, television, playing games, radio, conversation) should be avoided during the pre-ECG time window.

Continuous 24-hour ECGs are not planned for Part B of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.3.5. Heat Pain Threshold Test

Heat pain threshold tests will be conducted at the times indicated in the Schedule of Assessments (Appendix 6).

A computer-controlled thermal sensory analyzer device will be used to measure the heat pain threshold and tolerance level of the subjects. The heat pain assessments will be conducted on the subject's thigh.

Heat Pain Threshold:

For heat pain threshold measurements, the thermode will be placed directly on the skin of the right thigh, within an area selected before the start of the experiment and defined by surgical marking. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in

their dominant hand, to indicate when the heat pain threshold (first sensation of heat pain) is reached by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Heat Pain Tolerance:

For heat pain tolerance measurements, the thermode will be placed within the same surgically marked skin area of the anterior side of the right thigh, which was used to assess heat pain threshold. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in their dominant hand, to indicate when the heat-evoked pain has reached an intensity that is no longer tolerable, by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Safety Precautions

As there is a risk that OLP-1002 may affect the heat pain threshold, Covance CRU will put appropriate safety measures in place to ensure that subjects are not exposed to extremes of temperature when taking a shower or consuming hot drinks. During the heat pain safety assessments, the cut-off temperature for either test is 53 °C in order to prevent skin injury.

7.3.6. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

7.3.7. Body Weight and Height

Body weight (in underclothes) and height will be recorded at the times indicated in the Schedule of Assessments in Appendix 6. BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{body weight (kg)}}{(\text{height [m]})^2} \quad (\text{kg/m}^2)$$

7.3.8. Injection Site Assessments

Injection site assessments will be made at the times indicated in the Study Plan (Appendix 6).

Assessments will involve evaluation of the dosing site for the following criteria:

- Pain will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Requires medical intervention greater than analgesia

• Redness will be assessed by estimating the size of the red patch at the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm	51-100 mm	More than 100 mm	Requires medical intervention greater than analgesia

• Swelling will be assessed by estimating the size of the raised area around the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm and does not interfere with activity	51-100 mm or interferes with activity	More than 100 mm and prevents daily activity	Requires medical intervention greater than analgesia

In addition, how the swelling affects the subject in their daily routing activities will be considered.

• Tenderness will be evaluated using the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Mild pain to touch	Moderate Pain to touch	Severe pain to touch	Requires medical intervention greater than analgesia

- Bruising and ulceration will be evaluated as being present or absent.

Local tolerability ratings of ≥Grade 3 and the presence of ulceration will be recorded as an adverse event.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. In order to achieve PD endpoints in Part A, additional subjects will be included in 3 groups (8 subjects in total; 6 active: 2 placebo). Up to 3 additional groups may be added to Part A, consisting of either 4 subjects (3 active; 1 placebo) or 8 subjects (6 active; 2 placebo). Up to 3 additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.2. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of

OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

8.4. Pharmacodynamic Analyses

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned.

8.5. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- Mild: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but posing no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- Not Related: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- Unlikely Related: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- Related: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at the Follow-up visit will be followed up, where possible,

until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit (CRU). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Covance Drug Safety Services (DSS) Europe, Maidenhead, UK are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to DSS and the Sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Covance DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 2 working days of the initial notification to DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy reported by female subjects or

the female partners of male subjects should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total protein Urea	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[a]:	**Drug screen[b]:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test MDMA Alcohol breath test	Follicle-stimulating hormone[a] Serum pregnancy test (human chorionic gonadotropin)[a] Urine pregnancy test[c]

[a] Only analyzed at Screening.
[b] Only analyzed at Screening and Check-in.
[c] A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	19	76
Clinical laboratory evaluations (excluding serology)	7.5	6	45
Serology	3.5	1	3.5
Total:			124.5

Part B

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	29	116
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			194.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject during the study will not exceed that donated during a standard blood donation (approximately 500 mL).

Appendix 4: Contraception Guidance

Definitions

Females of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Females of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary (non-barrier) methods of contraception include:

- hormone injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - bilateral tubal ligation
    - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)

- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects can only choose a cervical cap or diaphragm if they have already had a prescription and fitting by their healthcare provider to ensure protocol requirements are met. Female subjects of childbearing potential should refrain from donation of ova from Check-in until 90 days after the Follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide
- vasectomised male subject (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success).

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the Follow-up visit.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the Follow-up visit.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a

public registry, all identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled and randomized subject, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

Study Plan – Part A (Single Dose)

	Pre-screening [d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Urine drugs of abuse screen		X	X							
Alcohol breath test		X	X							
Cotinine test		X	X							
Serology		X								
FSH and serum pregnancy test[a]		X								
Urine pregnancy test[a]			X							X
Informed consent	X	X								
Study residency:										
Check-in			X							
Check-out					Day 3 (48 hours postdose)					
Non-residential visit	X	X				X	X	X	X	X
Study drug administration:					Day 1 (0 hours)					
Safety and tolerability:										
Adverse event recording		X	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording		X	X	X	Ongoing	X	X	X	X	X

Supine blood pressure, pulse rate, respiratory rate, and body temperature		X			Predose, 1, 2, 4, 8, 24 (± 1 hour), and 48 hours postdose	X	X	X	X	X
	Pre-screening [d]	**Screening**	**Day -2**	**Day -1**	**Days 1 to 3**	**Day 4**	**Day 7 (± 2 days)**	**Day 10 (± 2 days)**	**Day 14 (± 2 days)**	**Poststudy (Day 28 ± 2 days)**
Supine 12-lead ECG		X			Predose, 4, 24 (± 1 hour) and 48 hours postdose		X		X	X
Continuous ECG extraction[b,c]				-24, -23.5, -23, -22.5, -22, -21.5, -21, -20, -18, -16, -12 hours	Day 1: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours					
Heat pain threshold test (heat pain threshold and heat pain tolerance)					Day 1: predose, 2, 4, 12, and 24 hours postdose (± 1 hour)					
Clinical chemistry, haematology, and urinalysis		X	X		48 hours postdose		X		X	X

Height and BMI		X								
Body weight		X	X							X
Physical examination		X								
Symptom-directed physical examination					Prior to discharge		X		X	X
	Pre-screening [d]	**Screening**	**Day -2**	**Day -1**	**Days 1 to 3**	**Day 4**	**Day 7 (± 2 days)**	**Day 10 (± 2 days)**	**Day 14 (± 2 days)**	**Poststudy (Day 28 ± 2 days)**
Injection site assessment					Predose, 1, 2, 4, 8, 24, 48 hours postdose		X		X	X
Pharmacokinetics[e]										
Blood sampling					Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose	X	X	X	X	X
Pharmacodynamics[d]:										
Intradermal capsaicin test (capsaicin-evoked pain and secondary hyperalgesia measurement)	X		X		Day 2 (The area of secondary area of hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection)					

Abbreviations: BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone.
[a] Female subjects only; a positive urine pregnancy test result will be confirmed with a serum pregnancy test.
[b] All times are relative to dosing with OLP-1002.
[c] Continuous ECG recording may begin at approximately 25 hours before dosing to allow for checks to be completed prior to the first extraction timepoint and will continue for 24 hours postdose, ie, until after the last timepoint for ECG extraction (24 hours postdose). At timepoints for ECG extractions, subjects will be supinely resting for a total of 15 minutes (10-minute supine rest period, 5-minute extraction). Data will be archived for potential future analysis and will not be available for review during the study.
[d] Pharmacodynamic assessment groups only.
[e] PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

Study Plan – Part B (Multiple Dose)

	Screening	Day -1	Days 1-15	Day 18 (± 2 days)	Day 22 (± 2 days)	Day 25 (± 2 days)	Day 29 (± 2 days)	Poststudy (Day 57 ± 2 days)
Inclusion/exclusion criteria	X							
Demographic data	X							
Medical history	X							
Urine drugs of abuse screen	X	X						
Alcohol breath test	X	X						
Cotinine test	X	X						
Serology	X							
FSH and serum pregnancy test[a]	X							
Urine pregnancy test[a]		X			X		X	X
Informed consent	X							
Study residency:								
Check-in		X						
Check-out			Day 15 (48 hours postdose)					
Non-residential visit	X			X	X	X	X	X
Study drug administration:			Days 1, 4, 7, 10, and 13					
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature	X		Day 1: predose, 1, 2, 4 and 8 hours postdose Day 2, Day 4 (postdose), Day 5, Day 7 (postdose), Day 9, Day 10 (postdose), Day 12, Day 13: predose, 1, 2, 4 and 8 hours postdose, and Day 15	X	X	X	X	X

	Screening	Day -1	Days 1-15	Day 18	Day 22	Day 25	Day 29	Poststudy (Day 57 ± 2 days)
Heat pain threshold test (heat pain threshold and heat pain tolerance)	X		Day 1 and Day 13: predose, 1, 2, 4, 8, 24 hours postdose					
Supine 12-lead ECG	X		Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Clinical chemistry, haematology, and urinalysis	X	X	Days 2, 5, 9, 12, 17		X		X	X
Height and BMI	X							
Body weight	X	X						X
Physical examination	X							
Symptom-directed physical examination			Days 1, 4, 7, 10, 13		X		X	X
Injection site assessment			Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Pharmacokinetics:								
Blood sampling[b]			Day 1 and Day 13: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose Days 4, 7, 10 Predose Day 15	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone.
[a] Female subjects only; a positive urine pregnancy test results will be confirmed with a serum pregnancy test.
[b] PK timepoints will be reviewed based on emerging data and may be updated.

Appendix 7: Protocol Amendment Summary of Changes

Protocol Amendment 5 (Version 4; 26 March 2019)

This substantial amendment has been issued to update the Principal Investigator from [redacted] to [redacted].

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**.

Title Page

Principal Investigator:
[redacted] was replaced by [redacted]

Investigator Agreement

[redacted] was replaced by [redacted]

Study Identification

[redacted] was replaced by [redacted]

Tel: [redacted] was replaced by [redacted]

Protocol Amendment 4 (Version 3; 29 January 2019)

This substantial amendment has been issued to update the female contraception criteria to allow female subjects to use alternative forms of contraception including the combined oral contraceptive pill, combined hormonal patch, and combined hormonal vaginal ring. Additionally, it has been clarified that only a serum pregnancy test will be conducted at Screening.

A detailed summary of changes is presented below. For each section, deleted text is shown in s~~trikethrough~~, and new text is shown in **bold**:

Appendix 4

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary ~~highly effective~~ and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary ~~highly effective~~ **(non-barrier)** methods of contraception include:

- **hormone injection (as prescribed)**
- **combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)**

- **combined hormonal patch (as prescribed)**
- **combined hormonal vaginal ring (as prescribed)**
- surgical method performed at least 3 months prior to the Screening visit:
  - bilateral tubal ligation
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)
- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Appendix 6

~~Hormone panel~~ was replaced by **FSH and serum pregnancy test** in the study plan for Part A and Part B for clarity.

A footnote was added to the study plan for Part A and Part B to specify that the FSH and serum pregnancy test will be conducted for female subjects only.

Urine pregnancy test at Screening removed for Part A and Part B.

Protocol Amendment 3 (Version 2.2; 12 December 2018)

This non-substantial amendment has been issued to include a clinical laboratory assessment on Day -2 in Part A.

Appendix 3

Additional clinical laboratory sample added to Part A. Total blood volume withdrawn in Part A updated to 124.5 mL.

Appendix 6 Study Plan (Part A)

Clinical chemistry, haematology, and urinalysis assessment added on Day -2.

Protocol Amendment 2 (Version 2.1; 29 November 2018)

This non-substantial amendment has been issued to correct minor inconsistencies in PK sampling timepoints, data cut off for dose escalation, clinical laboratory assessment timepoints, and the synopsis. Additionally, details of the injection site assessments have been added to the protocol.

A detailed summary of changes is presented below. For each section, deleted text is shown in s~~trikethrough~~, and new text is shown in **bold**:

Synopsis: Endpoints

Text added:

Safety:
Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, **heat pain threshold and tolerance,** and physical examinations.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from groups that received lower doses of OLP-1002.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day **10** (**216** hours postdose) from groups that received lower doses of OLP-1002.

Section 7.3.8

Entire section added to describe injection site assessments.

Appendix 3

Total blood volume for PK analysis (76 mL) added.

Appendix 6 - Schedule of assessments Part A

24 hour postdose continuous ECG recording timepoint added.

Appendix 6 - Schedule of assessments Part B

Clinical chemistry, haematology, and urinalysis for Days 1-15 previously read:

Days 2, 4, ~~7~~, ~~10~~,~~13~~

Clinical chemistry, haematology, and urinalysis for Days 1-15 now reads:

Days 2**, 5, 9, 12, 17**

PK blood sampling for Days 1-15 previously read:

Day 1 and Day ~~15~~: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, ~~8, 11, 15~~ Predose

PK blood sampling for Days 1-15 now reads:

Day 1 and Day **13**: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, **7, 10** Predose
Day 15

Protocol Amendment 1 (Version 2; 02 October 2018)

This amendment has been generated following the non-acceptance of the original protocol (version 1) by the Medicines and Healthcare products Regulatory Agency (MHRA) on 20 September 2018. All changes made have been in response to comments provided by the MHRA.

The primary changes in this amendment are:

1. Inclusion of PK sampling in Parts A and B:
    - PK objective and exploratory endpoints added (Section 2).
    - Discussion of PK included Section 3.4.
    - PK stopping criteria added to Section 3.7.
    - PK assessments included in Section 7.1.
    - PK population and analysis (Section 8.2.1).
    - Blood volumes updated to include samples for PK assessments (Appendix 3).
2. Exclusion and stopping criteria updated
    - Women who are pregnant or breastfeeding have been excluded from the study (Section 4.2).
    - Liver function tests, tachycardia, and hypertension stopping criteria have been updated (Section 3.7 and Section 4.4).
    - Stopping criteria for SAEs and serious AEs have been added (Section 3.7 and Section 4.4).
3. Safety, tolerability, and PK data up to Day 22 in Part B will be reviewed prior to dose escalation (Section 3.1.2).
4. Sentinel dosing included in Part B (Section 3.1.2).
5. It has been specified that the maximum dose for additional groups will not exceed 20 µg (Section 3.5.3).

Minor changes:

1. Additional clinical laboratory evaluations have been included on Day 14 in Part A.
2. The definition of the Safety population has been updated to include all subjects who receive OLP-1002.
3. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Section 1.6

Previously read:

This information, together with the pharmacodynamic (PD data, will help establish the doses and dosing regimen suitable for future studies in patients.

Now reads:

This information, together with the pharmacodynamic (PD) **and pharmacokinetic (PK)** data, will help establish the doses and dosing regimen suitable for future studies in patients.

Section 2.1

Objective added:

Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

Section 2.2.1

Endpoint added:

- **demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.**

Section 2.2.2

Endpoints added:

- **For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])**

- **AUC from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-tlast}}$) (actual and DN)**
- **maximum observed plasma concentration (C_{max}) (actual and DN)**

Secondary PK

- **time of the maximum observed plasma concentration (t_{max})**
- **apparent plasma terminal elimination half-life ($t_{1/2}$)**

- **For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:**

Primary PK

- **AUC over a dosing interval ($AUC_{0\text{-}\tau}$) (actual and DN)**
- **$AUC_{0\text{-}\infty}$ (actual and DN)**
- **C_{max} (actual and DN)**

Secondary PK

- **minimum observed plasma concentration (C_{min})**
- **t_{max}**
- **$t_{1/2}$**
- **observed accumulation ratio based on $AUC_{0\text{-}\tau}$ ($RAAUC_{0\text{-}\tau}$)**
- **observed accumulation ratio based on C_{max} (RAC_{max}).**
- **Temporal change parameter (TCP)**

Other PK parameters may also be added if deemed necessary.

Section 3.1.1

Previously read:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from the lower dose levels.

Now reads:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, **PK,** and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day **10** (**216** hours postdose) from the lower dose levels. **For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.**

Figure 1 – footnote

Text added:

Groups A9 to A11 may be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Figure 2 – footnote

Text added:

Groups B4 to B6 will be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Section 3.1.2

Previously read:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. ~~There will be no sentinel dosing in Part B.~~ For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from the lower dose levels. Part B may start after a review of the safety ~~and~~ tolerability for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Now reads:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from the lower dose levels. Part B may start after a review of the safety**,** tolerability**, and available PK data** for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Section 3.3

Previously read:

Following review of the safety, tolerability, and PD data, additional dose groups may be added to the study.

Now reads:

Following review of the safety, tolerability, **PK,** and PD data **(where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7])**, additional dose groups may be added to the study. **The maximum dose for any additional group will not exceed 20 µg.**

Section 3.4

Previously read:

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

~~Pharmacokinetic analysis will not be conducted in this study. T~~he bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose~~s~~ would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. ~~Thus, the additional burden of sampling procedures would not be justified by the quality of the data which it would generate.~~

Now reads:

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up

to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. **Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable.** It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. **In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.**

Section 3.4.1

Previously read:

In Part B, ~~all subjects in a group will be dosed on the same day~~. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3).

Now reads:

In Part B, **sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day**. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). **If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.**

Section 3.5.3

Text added:

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of ~~5~~ subjects, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002. **For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.**

In Part B, doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. **Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.**

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of **3 or 4** subjects**, respectively**, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Section 3.7

Previously read:

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in ~~liver function tests~~ ~~(~~aspartate aminotransferase, alanine aminotransferase~~,~~ alkaline phosphatase ~~and total bilirubin)~~ defined as 3 times the upper limit of normal in ~~3~~ or more subjects in a group ~~(~~confirmed with repeat testing~~)~~.

- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.

Now reads:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- **One or more subjects experience an SAE that is considered to be related to OLP-1002.**
- **Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.**
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase **or** alkaline phosphatase **(**defined as 3 times the upper limit of normal**), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be** confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- **The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).**

Section 4.2

Exclusion criteria added:

4. Female subjects who are pregnant or breastfeeding.

Section 4.4

Previously read:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal

Now reads:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal**, including:**
    - **a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),**
    - **severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),**
    - **elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),**
    - **QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),**
    - **Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),**
    - **Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).**

Section 7.1

Section added:

7.1 Pharmacokinetic Assessments

7.1.1 Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times

of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, only samples collected from subjects that received >12 µg OLP-1002 will be initially analyzed. If PK data is quantifiable at concentrations of OLP-1002 >12 µg, samples from lower dose groups will be retrospectively analyzed. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2 Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

Section 8.2

Previously read:

8.2.~~1~~ Pharmacodynamic population

The PD population will include all subjects who received at least 1 dose of ~~study treatment~~ OLP-1002 or placebo and for whom PD can be evaluated.

8.2.~~2~~ Safety Population
The safety population will include all subjects who received at least 1 dose of ~~study treatment~~ or placebo ~~and have at least 1 postdose safety assessment~~.

Now reads:

8.2.1 Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.**2** Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.**3** Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3 Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma and urine concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

Appendix 3

Table updated:

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis*	**4**	**19**	**76**
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			~~33.5~~**109.5**

Part B

	Volume per blood sample (mL)	**Maximum number of blood samples**	**Total amount of blood (mL)**
Pharmacokinetic analysis	**4**	**29**	**116**
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			~~78.5~~**194.5**

Appendix 6

PK and Blood sampling rows added to the schedule of events for Part A and Part B. In the Schedule of events for Part A, footnote e was added. In the Schedule of events for Part B, footnote b was added.

Clinical chemistry, hematology, and urinalysis was added to the Schedule of events for Part A on Day 14.

Protocol

OLP-1002 – A First-in-human, Double-blind, Placebo-controlled, Single and Multiple Subcutaneous Dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Male and Female Subjects

Protocol Status: Final
Protocol Date: 29 January 2019
Protocol Version: 3

Investigational Product: OLP-1002

Protocol Reference Number: OLP-1002-001
Covance Study Number: 8379789
EudraCT Number: 2018-003085-13

Sponsor:
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Sponsor Signatory:
[redacted]

Principal Investigator:
[redacted]

SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

Feb 01, 2019
Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

[redacted]

[redacted]
Principal Investigator

31 JAN 2019
Date

STUDY IDENTIFICATION

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SYNOPSIS

Title of study: OLP-1002 – A first-in-human, double-blind, placebo-controlled, single and multiple subcutaneous dose, safety, tolerability, pharmacokinetic, and pharmacodynamic study in healthy male and female subjects
Objectives: The primary objective of the study is to assess the safety and tolerability of single and multiple subcutaneous doses of OLP-1002 in healthy subjects. The exploratory objectives of the study are to evaluate the pharmacodynamic effect of OLP-1002 following single subcutaneous doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of a single subcutaneous doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.
Study design: This will be a double-blind, randomized, placebo-controlled, single and multiple subcutaneous dose study conducted in 2 parts, including healthy male and female subjects.
Number of subjects: Part A: 44 subjects will be studied in 8 groups (5 groups of 4 and 3 groups of 8). Part B: 24 subjects will be studied in 3 groups (Groups B1 to B3). Up to 24 additional subjects may be recruited into Part A and Part B of the study if required.
Diagnosis and main criteria for inclusion: Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 28.0 kg/m^2 (inclusive).
Investigational products, dose, and mode of administration: Test product: OLP-1002 Proposed dose levels for Part A: 30 ng, 120 ng, 400 ng, 1.2 µg, 3 µg, 6 µg, 12 µg, and 20 µg. Proposed dose levels for Part B: the doses for Part B will be decided in consultation with the Sponsor and on the basis of data from Part A of the study. The highest dose in Part B will be up to 50% of the highest dose in Part A. Administration route: subcutaneous
Reference product and mode of administration: Reference product: placebo Administration route: subcutaneous
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to Follow-up): approximately 8 weeks for Part A and approximately 12 weeks for Part B.

Endpoints:

Pharmacodynamics:

In Part A, the analgesic effect of OLP-1002 will be investigated in 3 groups consisting of 8 subjects (6 active: 2 placebo) using experimental capsaicin-evoked pain methods. Measurement of capsaicin-evoked pain will be performed at pre-screening, baseline and on Day 2, and secondary hyperalgesia at 5 and 30 minutes post-capsaicin injection. Continuous electrocardiogram (ECG) recording will be conducted to investigate the effect of OLP-1002 on cardiac function.

Safety:

Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, heat pain threshold and tolerance, and physical examinations.

Pharmacokinetics:

In Part A, the following PK parameters will be determined where possible: area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$), maximum observed plasma concentration (C_{max}), time of the maximum observed plasma concentration (t_{max}), and apparent plasma terminal elimination half-life ($t_{1/2}$). PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

In Part B, the following PK parameters will be determined where possible: AUC over a dosing interval ($AUC_{0-\tau}$), $AUC_{0-\infty}$, $C_{max,}$ minimum observed plasma concentration (C_{min}), t_{max}, $t_{1/2}$, observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$), observed accumulation ratio based on C_{max} (RAC_{max}), and Temporal change parameter (TCP). PK samples from all groups in Part B will be analyzed.

Statistical methods:

Pharmacodynamics:

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of pharmacodynamic data is planned.

Safety:

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

Pharmacokinetics:

Individual plasma concentrations and PK parameters of OLP-1002 will be listed and summarized using descriptive statistics. Individual and mean OLP-1002 concentration-time profiles will be presented graphically.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours postdose
BMI	body mass index
C_{max}	maximum observed plasma concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSA	clinical study agreement
DN	Dose normalized
DRG	dorsal root ganglion
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
E_{max}	maximum pain intensity
FCA	Freund's Complete Adjuvant
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia’s method
SAE	serious adverse event
SC	subcutaneous(ly)
SNL	spinal nerve ligation
$t_{1/2}$	elimination half-life
tE_{max}	time of maximum pain intensity
T_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
VAS	Visual Analogic Scale
VGSC	voltage-gated sodium channel

1. INTRODUCTION

1.1. Overview

OLP-1002 is a novel peptide nucleic acid (PNA) derivative which acts as a specific voltage-gated sodium channel (VGSC) protein ($Na_v1.7$) inhibitor, and is being developed by OliPass for the treatment of pain.

The $Na_v1.7$ protein is a subtype of VGSCs. $Na_v1.7$ is particularly important in nociception and pain signaling, with congenital loss-of-function mutations in $Na_v1.7$ resulting in the inability to experience pain. Selective $Na_v1.7$ inhibitors are believed to have the potential to treat severe pain safely[1]. The active sites of VGSC subtypes are virtually indistinguishable by their 3-dimensional structure and thus the discovery of selective $Na_v1.7$ small molecule inhibitors has been extremely challenging. Since inhibition of $Na_v1.5$ subtype elicits long QT cardiotoxicity, inhibition of $Na_v1.5$ subtype should be avoided at therapeutic doses.

To date, there are several $Na_v1.7$ inhibitors claimed to be selective that have been evaluated in human subjects:

- Vixotrigine (formerly known as raxatrigine) inhibits $Na_v1.7$ as well as other VGSC subtypes. Vixotrigine is in phase III clinical development for trigeminal neuralgia. Due to the limited $Na_v1.7$ selectivity over $Na_v1.5$, vixotrigine was evaluated primarily in patients with a low heart risk.
- Funapide is a $Na_v1.7$ inhibitor with limited $Na_v1.7$ selectivity, and was in phase IIb clinical trials as of July 2014. Although funapide showed analgesic activity in a small number of erythromelalgia patients, dose-limiting adverse events (AEs), including dizziness and somnolence, were observed[2]. The central nervous system (CNS) AEs were due to its poor $Na_v1.7$ selectivity.
- PF-05089771 is a $Na_v1.7$ selective inhibitor with a claimed $Na_v1.7$ selectivity of > 2000-fold versus other subtypes of sodium channel and was evaluated in patients of erythromelalgia or dental pain. It is thought low drug concentrations achieved in the target tissue could be a possible explanation for its poor analgesic activity in human patients[3].

OLP-1002 is fully complementary to a 14-mer RNA sequence spanning the junction of intron 4 and exon 5 in the human SCN9A pre-mRNA which codes for the $Na_v1.7$ channel. OLP-1002 yields SCN9A mRNA splice variant(s) encoding variant $Na_v1.7$ protein(s) lacking the sodium channel activity (ie, a non-functional channel), thereby inhibiting $Na_v1.7$ channel function.

1.2. Summary of Nonclinical Pharmacology

1.2.1. In Vitro Pharmacology Studies

Overall, results from the in vitro pharmacology studies showed OLP-1002 elicits responses consistent with its designed function[4]. It inhibits SCN9A mRNA expression and yields the

$Na_v1.7$ variant protein or proteins lacking sodium channel activity. Its effects are highly selective, which may provide for an improved margin of safety compared to other $Na_v1.7$ inhibitors.

OLP-1002 at 1 to 100 zM in PC3 prostate carcinoma cells induced exon skipping and yielded SCN9A mRNA splice variant(s) encoding a $Na_v1.7$ variant protein or proteins lacking sodium channel activity.

In rat dorsal root ganglion (DRG) neuronal cells, OLP-1002 at 1000 zM inhibited $Na_v1.7$ protein expression by > 50%, while OLP-1002R at 100 and 1000 zM inhibited $Na_v1.7$ expression almost completely. As OLP-1002R is fully complementary to rat SCN9A pre-mRNA, OLP-1002R would be predicted to be more potent than OLP-1002 in this cell type.

SCN9A mRNA expression level was evaluated by quantitative polymerase chain reaction (qPCR). OLP-1002 inhibited the expression of the SCN9A mRNA in PC3 cells with sub-attomolar potency.

In SH-SY5Y human neuroblastoma cells stimulated with tumor necrosis factor (TNF)-1α to upregulate the expression of SCN9A mRNA, OLP-1002 decreased expression by 46% to 49% at 1 fM to 10 pM. In rat DRG neuronal cells, OLP-1002 at 1 fM significantly decreased SCN9A mRNA expression by 54%.

In rat DRG neuronal cells, OLP-1002 markedly and significantly inhibited the sodium current by 77% at 0.1 aM and 73% at 1 aM, while for OLP-1002R, the inhibition was 66% at 0.1 aM and 70% at 1 aM. Given that rat DRG neuronal cells express various subtypes of sodium channel, the observed inhibitions of 66% to 77% correspond to the complete knockout of the $Na_v1.7$ sodium channel subtype with OLP-1002 or OLP-1002R.

The $Na_v1.7$ selectivity over $Na_v1.5$ was evaluated in H9C2 rat cardiomyocytes which are known to abundantly express the rat $Na_v1.5$ sodium channel subtype. Following incubation with OLP-1002 or OLP-1002R at 1 aM or 1 pM, there were no notable decreases in the sodium current. Considering that OLP-1002 and OLP-1002R inhibit the expression of $Na_v1.7$ protein at 1 aM or lower in rat DRG neuronal cells, the $Na_v1.7$ selectivity of OLP-1002 and OLP-1002R over $Na_v1.5$ is estimated to be in excess of one million-fold. Such a large $Na_v1.7$ selectivity over $Na_v1.5$ has not been realized with small molecule $Na_v1.7$ inhibitors, suggesting that OLP-1002 potentially offers pain management with much greater cardiovascular safety.

1.2.2. In Vivo Pharmacology Studies

Spinal nerve ligation (SNL) has been widely applied as a rat model for neuropathic pain. OLP-1002 and OLP-1002R were found to be very potent, but highly variable in potency, in reversing neuropathic allodynia in this model. Analyses of the therapeutic potency strongly suggested that a marked proportion of subcutaneously (SC) administered OLP-1002 or OLP-1002R may have been topically delivered directly to the spinal nerves exposed in the dorsal cavity created during the SNL modelling. In addition, the variability of the therapeutic potency may be due to a variable degree of healing of the SNL surgery wound. If an animal

recovers slowly, the animal tends to be left with a dorsal cavity. Therefore, estimations of potency in these studies with this model should be treated with caution.

In one study using the SNL model, allodynia in rats was slowly and gradually reversed by OLP-1002 SC administered at nominal doses of 1, 3, and 6 pmol/kg once every 2 days (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). As the onset time for pain reduction was 4 days, the doses used were not sufficient for fast onset of activity. In this study, the animals should have reasonably recovered from the dorsal wound, and therefore less susceptible to topical delivery directly to the exposed spinal nerves. However, in another study in this model, when OLP-1002 was intraperitoneally (IP) administered once every 3 days to avoid the likelihood of local delivery to the spinal nerves, OLP-1002 surprisingly reversed the allodynia at 5 fmol/kg, and was superior or comparable to pregabalin 30 mg/kg, a gold standard for neuropathic pain studies. The high potency shown at 5 fmol/kg IP strongly suggests the possibility that OLP-1002 is efficiently absorbed by the enteric nervous system, travels to the spinal cord, and then redistributes to the spinal nerves of the SNL ligation. This opens the possibility of efficient oral delivery of OLP-1002 to the spinal cord.

When evaluated for their ability to reverse the inflammatory pain in rats inflicted with Freund's Complete Adjuvant (FCA)-induced severe paw inflammation, OLP-1002 at 300 pmol/kg and OLP-1002R at 100 pmol/kg significantly reversed the thermal hyperalgesia, and both were more effective than pregabalin 30 mg/kg.

Paw burn injury induces hyperalgesia in rats and is known to upregulate $Na_v1.7$ expression in the L5 and L6 DRGs of the affected side. Burn injury induces a far weaker degree of paw inflammation than FCA-induced paw inflammation. OLP-1002 SC administered inhibited the thermal hyperalgesia in paw burn injury in a dose-dependent manner. At 25 fmol/kg, OLP-1002 did not inhibit thermal hyperalgesia. Although OLP-1002 at 625 fmol/kg significantly inhibited the thermal hyperalgesia, the efficacy was moderate and weaker than pregabalin 30 mg/kg. This suggests that SC dosing does not offer the local topical delivery to spinal nerves in this model as seen in rats without a dorsal cavity wound. In this study, the $Na_v1.7$ expression in the DRG of the burn injury side significantly decreased by 58% with 625 fmol/kg OLP-1002, validating the target engagement for analgesic activity.

An intraplantar injection of formalin induces severe acute pain. The contributors to acute pain are known to be complex and require further elucidation. However, acute peripheral inflammation is known to contribute much to Phase II Pain (pain from 10 to 40 min after the formalin injection). In this model, OLP-1002 significantly inhibited Phase II Pain at comparable or saturated efficacy when SC administered at 10 to 100 pmol/kg (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). Thus peripheral acute inflammatory pain could be treated with 10 pmol/kg or less.

1.2.3. Ex Vivo Pharmacology Studies

One day post-SC injection, OLP-1002 and OLP-1002R at 100 pmol/kg significantly inhibited the expression of $Na_v1.7$ protein by 39% and 57%, respectively, in the spinal cord of rats subjected to SNL.

In other rats subjected to SNL, OLP-1002R slowly and gradually reversed the allodynia in a dose-dependent manner. OLP-1002R at 30 fmol/kg (the highest dose administered) had the greatest effect, but the dose was not high enough to elicit full therapeutic efficacy. OLP-1002R inhibited expression of $Na_v1.7$ protein in these animals, most notably at 1 fmol/kg, and decreased SCN9A mRNA expression by approximately 40% at 1 to 30 fmol/kg. The observed inhibitions were largely consistent with the in vivo therapeutic activity findings.

Taking all the in vivo and ex vivo findings together, OLP-1002R was concluded to inhibit neuropathic allodynia by inhibiting the expression of the SCN9A mRNA and the $Na_v1.7$ protein.

1.3. Summary of Safety Pharmacology

In vitro, OLP-1002 did not inhibit the human ether-à-go-go-related gene (hERG) channel current expressed in human embryonic kidney (HEK) cells at the highest concentration tested 2 μM (the limit of the validated analytical method for OLP-1002).

In the in vivo safety pharmacology studies, OLP-1002 SC administered at dose levels up to 100 nmol/kg had no effect on body temperature, neurological function, or respiratory function in rats, and had no significant toxic effect on cardiovascular function in cynomolgus monkeys.

1.4. Summary of Toxicology

In rats, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included pigment accumulation in the kidney of males administered 100 nmol/kg/dose and females administered ≥ 10 nmol/kg/dose, foreign material and vacuolated macrophage infiltrates in males and/or females administered ≥ 1 nmol/kg/dose, and an increased incidence and/or severity of mononuclear cell infiltrates at the injection sites in males and/or females administered ≥ 10 nmol/kg/dose. These findings persisted through the recovery phase in animals administered 100 nmol/kg/dose. However, the effects were considered non-adverse due to their mild severity and lack of impact on animal health and wellbeing. The no-observed-adverse-effect level (NOAEL) was 100 nmol/kg/dose. This dose level corresponded to maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from 0 to 24 hours postdose (AUC_{0-24}) values of 27.6 ng/mL and 174 ng·hr/mL, respectively, in males and 24.9 ng/mL and 128 ng·hr/mL, respectively, in females on Day 88 of the dosing phase.

In cynomolgus monkeys, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included mononuclear cell infiltrates at the SC injection sites of animals administered ≥ 10 nmol/kg/dose. This finding was not resolved with the completion of the recovery phase. However, the effects of 100 nmol/kg/dose were considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing. The NOAEL was 100 nmol/kg/dose (equivalent to 462.29 μg/kg/dose), which corresponded to C_{max} and AUC from 0 to 72 hours postdose (AUC_{0-72}) values of 121 ng/mL and 2840 ng·hr/mL in males, respectively, and 216 ng/mL and 4840 ng·hr/mL in females, respectively, on Day 88 of the dosing phase.

The genotoxic and mutagenic potential of OLP-1002 was evaluated with standard Good Laboratory Practice (GLP) via in vitro bacterial mutagenicity and chromosomal aberration studies, and was found to be negative.

1.5. Summary of Nonclinical Pharmacokinetics

In rats, following a single SC dose of ^{14}C-OLP-1002, the time of maximum observed concentration (T_{max}) was 0.5 to 1 hour for both radioactivity and parent compound. Plasma concentrations of total radioactivity were quantifiable through the last sampling time of 72 hours postdose, but was variable for the parent compound. The elimination half-life ($t_{1/2}$) of total radioactivity from plasma was 23 hours. Total radioactivity distributed into tissues, including those of the CNS protected by the blood-brain barrier. ^{14}C-OLP-1002-derived total radioactivity was not rapidly excreted from rats, with minimal amounts present in urine and feces. The bulk of the total radioactivity remained in carcasses, primarily in kidneys (cortex and medulla) and liver. Parent ^{14}C-OLP-1002 was present in plasma and tissues, but concentrations declined over time and were substantially lower than total radioactivity concentrations at the later sampling times.

After a single SC administration of ^{14}C-OLP-1002 to rats, the highest concentrations of total radioactivity were retained predominantly in the liver (10.4% to 13.3% of the dose), kidney cortex (3.47% to 4.96%), and kidney medulla (1.10% to 1.59% of the dose) through 168 hours postdose. For all other tissues, the total amounts of total radioactivity were substantially less, ranging from 0.0000203% in the 5th DRG to 0.327% in the spleen. Radioactivity was excreted slowly via both the renal and fecal routes of elimination. Total average recoveries of radioactivity in urine and feces through 336 hours postdose accounted for 2.31% and 1.75% of the administered radioactivity, respectively. The bulk of the administered total radioactivity was retained in the rat carcasses through 168, 336, 504, and 840 hours postdose. The kidney cortex, kidney medulla, and liver were the 3 tissues that retained the greatest amounts of the administered radioactivity.

Following a 16.1-µg/kg dose in rats, the plasma concentrations were still quantifiable at 72 hours postdose and the rate of elimination was slow, with $t_{1/2}$ 17.5 hours. It was not possible to accurately define the elimination phase for the 2.67- and 5.28-µg/kg dose levels.

In cynomolgus monkeys, following a single SC dose of ^{14}C-OLP-1002, T_{max} ranged from 0.25 to 1 hour for both total radioactivity and parent compound. Concentrations of total radioactivity were sustained in blood and plasma through the last sampling time of 144 hours postdose. Concentrations of parent compound were sustained in plasma through the last sampling time of 144 hours postdose in 2 of 3 monkeys, and were similar to plasma total radioactivity concentrations at 8 hours postdose. From 24 to 144 hours postdose, plasma concentrations of total radioactivity were substantially higher than for parent ^{14}C-OLP-1002 plasma concentrations.

The mean C_{max} of parent ^{14}C-OLP-1002 in plasma was 1.96 ng/mL. The mean plasma T_{max} was 0.833 hours. Plasma exposure of parent ^{14}C-OLP-1002 based on AUC extrapolated to infinity ($AUC_{0-\infty}$), was 12.7 ng·h/mL. After reaching C_{max}, plasma concentrations of parent ^{14}C-OLP-1002 declined with a mean $t_{1/2}$ of 84 hours.

1.6. Study Rationale

This is the first time OLP-1002 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data when OLP-1002 is administered SC as single and multiple doses to healthy subjects. This information, together with the pharmacodynamic (PD) and pharmacokinetic (PK) data, will help establish the doses and dosing regimen suitable for future studies in patients. The analgesic effects of OLP-1002 on a capsaicin-induced pain model will also be investigated.

1.7. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. For subjects in the PD assessment groups in Part A there will be some additional discomfort from the capsaicin test. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with OLP-1002 may be found in the Investigator's Brochure[4].

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is to assess the safety and tolerability of single and multiple SC doses of OLP-1002 in healthy subjects.

The exploratory objectives of the study are to evaluate the PD effect of OLP-1002 following single SC doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of single SC doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- incidence and severity of AEs
- vital signs measurements (blood pressure, pulse rate, respiratory rate)
- 12-lead electrocardiogram (ECG) parameters
- incidence of clinical laboratory abnormalities, based on clinical chemistry, hematology, and urinalysis test results
- physical examinations
- injection site assessment.

- demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.

2.2.2. Exploratory Endpoints

The following exploratory objectives will be assessed:

- pain intensity and duration will be assessed by AUC, maximum pain intensity (E_{max}), and time of maximum pain intensity (tE_{max}), calculated using a capsaicin-evoked pain model. The exploratory endpoint of secondary hyperalgesia will be assessed by the area of secondary area of hyperalgesia (Part A only).
- continuous (24-hour) ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval (Part A).
- heat pain threshold measurements and heat pain tolerance measurements.
- For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:

  Primary PK

  - area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])
  - AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)
  - maximum observed plasma concentration (C_{max}) (actual and DN)

  Secondary PK

  - time of the maximum observed plasma concentration (t_{max})
  - apparent plasma terminal elimination half-life ($t_{1/2}$)
- For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:

  Primary PK:

  - AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)
  - $AUC_{0-\infty}$ (actual and DN)
  - C_{max} (actual and DN)

  Secondary PK

  - minimum observed plasma concentration (C_{min})
  - t_{max}
  - $t_{1/2}$
  - observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)
  - observed accumulation ratio based on C_{max} (RAC_{max}).
  - Temporal change parameter (TCP)

Other PK parameters may also be added if deemed necessary.

3. INVESTIGATIONAL PLAN

This will be a double-blind, randomized, placebo-controlled, single and multiple SC dose study conducted in 2 parts.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, PK, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

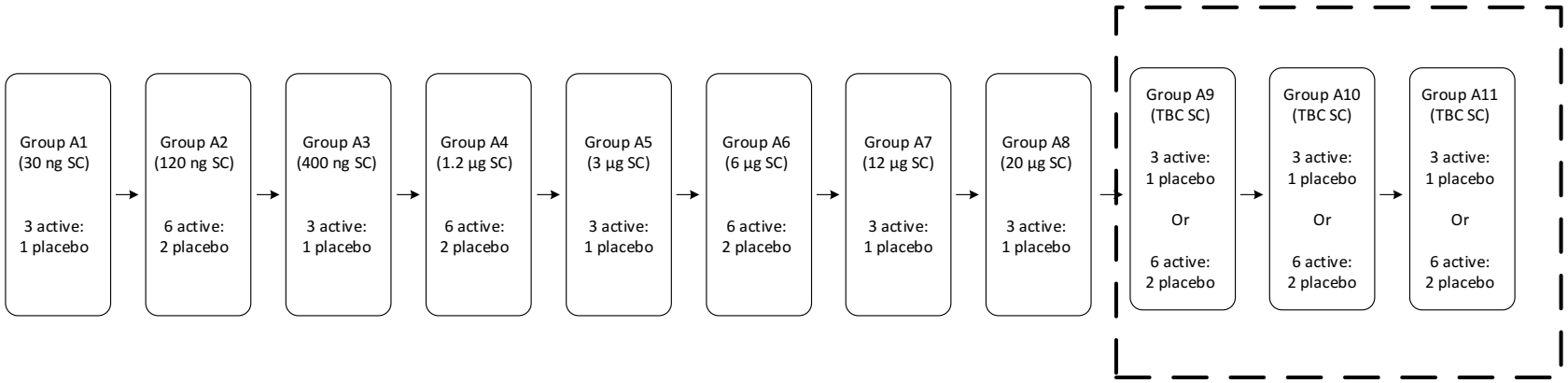
Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 10 (216 hours postdose) from the lower dose levels. For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.

In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, and A6 will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.

Sentinel dosing will be employed for all groups in Part A. To maintain the blind in a 4-subject group, the first subject will be dosed 48 hours before the second subject, and the second subject will be dosed 48 hours prior to the third and fourth subjects. In PD assessment groups, 2 subjects (1 active: 1 placebo) will be dosed 48 hours before the remaining 6 subjects (5 active: 1 placebo).

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic (Part A)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
Groups A9 to A11 may be included if required; dose levels will not exceed the maximum proposed dose of 20 µg.
Three groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

3.1.2. Part B

Part B will comprise a multiple-dose, sequential-group study. Overall, 24 subjects will be studied in 3 groups (Groups B1 to B3), with each group consisting of 8 subjects. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety and tolerability (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15.

All subjects will return for non-residential visits on Days 18 (± 2 days), 22 (± 2 days), 25 (± 2 days), and 29 (± 2 days), and for a poststudy visit on Day 57 (± 2 days).

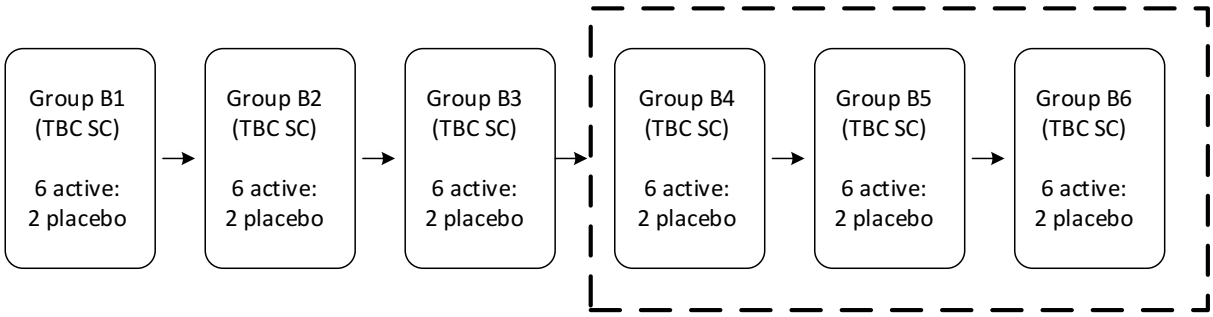
In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from the lower dose levels. Part B may start after a review of the safety, tolerability, and available PK for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

An overview of the study design is shown in Figure 2.

Figure 2: Study Schematic (Part B)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
All doses will be confirmed based on results of Part A; dose levels will not exceed the maximum proposed dose of 20 µg.
Groups B4 to B6 will be included if required.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 12 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Start of Study and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, PK, and PD data (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7]), additional dose groups may be added to the study. The maximum dose for any additional group will not exceed 20 µg. Up to 3 further groups of 8 subjects (6 active: 2 placebo) may be included in Part A, and up to 3 additional groups of 8 subjects (6 active: 2 placebo) may be included in Part B. The requirement for additional groups will be agreed with the Sponsor and documented in the Trial Master File (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential-group, ascending-dose design has been chosen for safety reasons as OLP-1002 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Subcutaneous doses have been chosen for both parts of the study, as this is the intended clinical route of administration.

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of

OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses < 12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore, if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.

This study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Continuous ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing in Part A for groups consisting of 4 subjects will be such that there will be 48 hours between the first and second subjects, and 48 hours between the second and remaining 2 subjects in each group. For groups in Part A consisting of 8 subjects, 2 subjects (1 active: 1 placebo) will be dosed 48 hours prior to the remaining 6 subjects.

In Part B, sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.

In Parts A and B, there will be a minimum interval of a 10-minute gap between dosing subjects (when dosed on the same day). Continuation to dose the remaining subjects in a group will be at the Investigator's discretion.

3.4.2. Pharmacodynamic Assessment

Pharmacodynamic assessments will be conducted for subjects in Groups A2, A4, and A6.

Human experimental pain models using healthy volunteers can be used to assess the effect of a drug or treatment under controlled clinical conditions. Capsaicin is a vanilloid responsible for the pungent taste of hot peppers. In mammalian species, capsaicin-induced pain is mediated through Group C nerve fibers following activation of vanilloid 1 transient receptor potential (TRPV1) channels[5]. $Na_v1.7$ has been implicated in controlling neuropeptide release from C-fibers, and suppression of capsaicin-induced neurogenic flair has been demonstrated by an $NA_v1.7$ inhibitor[6].

Several studies have used intradermal capsaicin for human experimental pain studies[7,8]. It has been possible to demonstrate dose-dependent responses, with intradermal injections of 100 µg generally agreed to be the ideal dosage for these studies. Intradermal injection of capsaicin causes a brief stinging/burning pain at the injection site (spontaneous pain) followed by development of secondary hyperalgesia, which can be assessed using equipment such as Von Frey hairs. A study by Gazerani et al.[5] found that the response was site-specific and while peak pain intensity and duration were greatest in the forehead it was found that areas of visible flare and secondary hyperalgesia were significantly larger in the forearm, making the forearm the most suitable site for experimentation.

Covance CRU, Leeds, UK in 2009 performed a validation study using intradermal capsaicin (Covance CRU Study: 9999-004) with between-subject and within-subject variability demonstrating that the assessments can be reliably conducted to assess pharmacological response.

For these reasons, it has been decided to:

- Measure both capsaicin-evoked pain and secondary hyperalgesia.
- Limit the number of capsaicin tests to 3 for each subject (pre-screening, baseline, and 48 hours postdose)
- Exclude subjects who have pain < 3 or > 9 (using a Visual Analogic Scale [VAS]) at the pre-screening visit from PD assessment groups.

3.5. Selection of Doses in the Study

3.5.1. Starting Dose

The rat has been identified as the most sensitive species in a 13-week SC toxicity study with a 4-week recovery phase (Covance study no. 8355564). The NOAEL was the 100 nmol/kg/dose (462.29 µg/kg/dose). This dose level resulted in C_{max} of 27.6 ng/mL and 24.9 ng/mL in males and females, respectively, and AUC_{0-24} of 174 ng.h/mL and 128 ng.h/mL in males and females, respectively[4]. As the exposure was lower in the female rats these data have been used to calculate the safety margins.

The dose of 462.29 µg/kg/dose corresponds to human equivalent doses (HEDs) of 74.8 µg/kg/dose, which gives a maximum recommended starting dose (MRSD) of 444 µg for a 60-kg human and thus a 15000-fold safety margin to the proposed starting dose of 30 ng and 22-fold margin to the proposed maximum dose of 20 µg. Additionally the NOAEL dose in the cynomolgus monkey was identified as 100 nmol/kg/dose (462.29 µg/kg/dose), which gives a higher HED of 150 µg/kg/dose.

In vivo, doses of 10 pmol/kg/dose (0.0462µg/kg/dose) or less were found to inhibit peripheral acute inflammatory pain. The equivalent human dose for a 60-kg human is 44 ng, thus a dose at which minimal biological effect is anticipated has been selected as the starting dose of 30 ng.

3.5.2. Exposure

Human exposures have been estimated from the pharmacokinetics in the cynomolgus monkey since a non-human primate represents the most closely related species. Approximately dose-proportional exposure was seen in the 13-week toxicity study (Covance study no. 8355565) and ^{14}C pharmacokinetic study (Covance study no. 8355568) over a dose range of approximately 1.1 to 100 nmol/kg (5.06 to 462.29 µg/kg)[4]. However, the lowest dose (5.06 µg/kg) from the ^{14}C study has been used to estimate the human exposures as it is closest to the proposed human dose range and has the sufficient quantifiable data.

The assumptions made in the human exposure estimation were that human exposure would be similar to the cynomolgus monkey and that exposure would be linear with dose. Following a dose of 5.06 µg/kg in the cynomolgus monkey, the C_{max} was 1.96 ng/mL and $AUC_{0-\infty}$ was 12.7 ng.h/mL. The extrapolated exposures at the planned human doses are shown in Table 1 with margins calculated to the exposures at the NOAEL in the female rat.

Table 1: Estimated Human Exposure and Safety Margins to the NOAEL in the Female Rat for Single Dose Administration of OLP-1002

Human dose		Single dose to human		Safety margins for single dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\infty}$
0.03	0.000500	0.000194	0.00125	129000	102000
0.12	0.00200	0.000775	0.00502	32100	25500
0.4	0.00667	0.00258	0.0167	9640	7650
1.2	0.0200	0.0077	0.0502	3210	2550
3	0.0500	0.0194	0.125	1290	1020
6	0.100	0.0387	0.251	643	510
12	0.200	0.0775	0.502	321	255
20	0.333	0.129	0.837	193	153

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

The dosing interval currently anticipated for the multiple-ascending-dose part of this study is 72 hours or 96 hours. Thus the average dosing interval (82 hours) is similar to the half-life determined in the monkey ^{14}C study of 84 hours. Dosing at approximately once per half-life would be anticipated to result in accumulation of around 2-fold. However, higher levels of accumulation were observed (2.28-fold for C_{max} and 3.76-fold for AUC_{0-24}) on Day 88 at the top dose group (100 nmol/kg, 462.28 µg/kg) in the 13-week cynomologus monkey toxicity study following twice-weekly dosing (every 72 or 96 hours). Calculations were performed to estimate the likely human half-life using a standard 1-point allometric approach from the ^{14}C cynomolgus monkey pharmacokinetic study data. The exponents used were 0.75 for apparent total plasma clearance (CL/F) and 1 for apparent volume of distribution (V_z/F) values combined with the average body weight of the animal (3.1 kg) and scaling to a 60 kg human [9–11]. This resulted in a human half-life estimate of 180 h which in turn gave an accumulation estimate of 3.7-fold based upon a dosing interval of 82 h. This further supports the use of the greater than 2-fold accumulation from the 13-week cynomolgus study to estimate exposure following multiple dosing. Multiplication of the exposure estimates for the single ascending

dose by 2.28 for C_{max} and 3.76 for AUC resulted in exposure estimates for multiple dosing presented in Table 2.

Table 2: Estimated Human Exposure and Safety Margin to the NOAEL in the Female Rat for Multiple Dose Administration of OLP-1002

Human dose		Multiple dose to human		Safety margins for multiple dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\tau,ss}$
0.03	0.000500	0.000442	0.00472	56000	27000
0.12	0.00200	0.00177	0.0189	14100	6800
0.4	0.00667	0.00589	0.0629	4230	2030
1.2	0.0200	0.017663	0.189	1410	680
3	0.0500	0.0442	0.472	560	270
6	0.100	0.0883	0.944	282	136
12	0.200	0.177	1.89	141	68
20	0.333	0.294	3.15	85	41
30	0.500	0.442	4.72	56	27

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

3.5.3. Proposed Doses

The proposed IMP dose levels for Parts A and B are shown in Table 3.

Table 3: Proposed Investigational Medicinal Product Dose Levels for Parts A and B

Study Part	Group	Dose (OLP-1002)
Part A	A1	30 ng or placebo
	A2	120 ng or placebo
	A3	400 ng or placebo
	A4	1.2 µg or placebo
	A5	3 µg or placebo
	A6	6 µg or placebo
	A7	12 µg or placebo
	A8	20 µg or placebo
	A9*	TBC or placebo
	A10*	TBC or placebo
	A11*	TBC or placebo
Part B	B1	TBC or placebo
	B2	TBC or placebo
	B3	TBC or placebo
	B4*	TBC or placebo
	B5*	TBC or placebo
	B6*	TBC or placebo

Abbreviations: TBC = to be confirmed
* groups to be included if required.

In Parts A and B, there should not be an increase of > 3-fold between dose levels above 120 ng.

For Part B, dose levels, dosing frequency, and dosing duration will be decided, in consultation with the Sponsor, on the basis of data from Part A of the study. Since predictions of human exposure of OLP-1002 suggest that OLP-1002 concentrations may be not be quantifiable and human data have been estimated from a single species, it is proposed that the highest dose in the multiple-ascending-dose part will be up to 50% of the highest dose in the single-ascending-dose part (ie, if the highest dose in the single-ascending-dose part is 20 µg, the highest dose in the multiple-ascending-dose part will be 10 µg). Therefore, if the predicted accumulation of 3.7-fold occurs, the highest exposure in the multiple-ascending-dose part will not exceed ~2-fold the maximum exposure in the single-ascending-dose part.

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

3.6. Dose Escalation

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 10 (216 hours postdose) from groups that received lower doses of OLP-1002. For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of 3 or 4 subjects, respectively, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

The justification for this is as follows:

- The study drug is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.

- A minimum of 3 subjects receiving the active drug is considered sufficient to characterize the safety profile for OLP-1002.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarizing results from all available safety assessments, will be sent to the Sponsor and a dose-escalation meeting will occur prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PD data may also be reviewed on an ongoing basis. In the event of a disagreement between Sponsor and Investigator on the dose-escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- One or more subjects experience an SAE that is considered to be related to OLP-1002.
- Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase (defined as 3 times the upper limit of normal), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥ 1 subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥ 1 subject in a group.
- The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).

If the sponsor deems it appropriate to resume dosing after the internal safety review, it can be done after the approval of a substantial protocol amendment.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Healthy male or females of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) between 18.0 and 28.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, single 12-lead ECG (resting heart rate > 45 bpm and < 90 bpm), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening as assessed by the Investigator (or designee).
4. Willing to abide by the contraception requirements as detailed in Appendix 4.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Any of the following:
    - QTcF > 450 ms confirmed by repeat measurement.
    - QRS duration > 110 ms confirmed by repeat measurement.
    - PR interval > 220 ms confirmed by repeat measurement.
    - findings which would make QTc measurements difficult or QTc data uninterpretable.
    - history of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
4. Female subjects who are pregnant or breastfeeding.
5. History of alcoholism or drug/chemical abuse within 1 year prior to Screening.

6. Alcohol consumption of > 21 units per week for males and > 14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
7. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
8. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2).
9. Active skin conditions such as dermatitis, allergy, eczema, psoriasis, or abnormal healing.
10. Tattoos, scars, or moles that in the opinion of the Investigator are likely to interfere with dosing or study assessments at any of the potential injection sites.
11. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days or 5 half-lives of the investigational product, whichever is longer, prior to Check-in.
12. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
13. Use or intend to use any prescription medications/products other than hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptive concomitant medications within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
15. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and/or Sponsor have given their prior consent.
16. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in.
17. Receipt of blood products within 60 days prior to Check-in.
18. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
19. Poor peripheral venous access.
20. Have previously completed or withdrawn from this study or any other study investigating OLP-1002, and have previously received the investigational product.
21. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
22. Part A – PD assessment groups only
    - Subjects considered non-acceptable responders to the intradermal capsaicin test at screening, defined as maximum VAS score of < 3.0 or > 9.0.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number at the time of their randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A, Subjects 101, 102, etc., in Part B Subjects 201, 202, etc.). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal, including:
    - a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),
    - severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),
    - elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),
    - QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),
    - Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),
    - Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Vials of OLP-1002 Injection Solution 100 µg/mL (1.5 mL in 5-mL vials) and the Diluent for OLP-1002 Injection Solution (5 mL in 10-mL vials) will be supplied by the Sponsor, along with the batch/lot number and Certificate of Analysis. The Diluent for OLP-1002 Injection Solution will also be used as the Placebo formulation. A certificate of batch certification and release, authorized by a Qualified Person in the European Union (EU) will also be issued, by a Covance CRU Qualified Person, for each batch of IMP imported into the EU.

The IMPs will be stored according to the instructions on the label at the CRU in a location that is locked with restricted access.

Dose solutions (OLP-1002 Injection Solution diluted with the Diluent for OLP-1002 Injection Solution) will be prepared by Covance CRU Pharmacy staff in accordance with instructions provided in the Pharmacy Manual. The Placebo formulation will be the Diluent for OLP-1002 Injection Solution without further manipulation.

5.2. Study Treatment Administration

Subjects will be administered the IMP in numerical order. OLP-1002 will be administered by SC injection in the upper arm. If subcutaneous dosing of OLP-1002 in the upper arm is not possible, the subject may be dosed in the abdomen at the Investigator's discretion. For subjects in Groups A2, A4, and A6, dosing will be on the opposite arm to the intradermal capsaicin test.

5.3. Randomization

The randomization code will be produced by the statistics department at Covance using a computer-generated pseudo-random permutation procedure. In Part A, 1 subject in groups

consisting of 4 subjects, and 2 subjects in groups consisting of 8 subjects, will be randomly assigned to receive placebo. In Part B, 2 subjects per group will be randomly assigned to receive placebo. All other subjects in a group will be randomized to receive OLP-1002.

Prior to the start of the study, a copy of the master randomization code will be supplied into the Covance CRU pharmacy staff (in sealed envelopes).

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo solution will be identical in appearance to the OLP-1002.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

To maintain the blind, the Investigator will be provided with sealed randomization code-break envelopes for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose-escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

All doses of IMP will be administered by suitably qualified study site staff.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription medications/products from 14 days prior to dosing until the Follow-up visit, and non-prescription medications/products from 7 days prior to dosing until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests. On dosing days, subjects will receive a light breakfast approximately 2 hours prior to dosing. Meals will be provided as appropriate at other times and water will be freely available at all times.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until the Follow-up visit.

Xanthine-containing foods and beverages will not be allowed from 36 hours before Check-in until Discharge from the site. Xanthine-containing foods and beverages will also not be allowed form 36 hours before non-residential site visits.

Chili pepper/hot sauce will not be allowed for 48 hours prior to Check-in for all subjects. Subjects in Groups A2, A4, and A6 will not be allowed chili pepper/hot sauce for 48 hours prior to their pre-screening visit.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until Discharge. Following discharge, up to 2 units/day of alcohol are permitted until 36 hours before each non-residential visit and the Follow-up visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 3 days before Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during this

time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit. Subjects should not be in receipt of blood products for 60 days prior to check-in.

6.6. Other Restrictions

Subjects in Groups A2, A4, and A6 will not be allowed to shower within 1 hour prior to the capsaicin-evoked pain tests at prescreening, predose, and postdose.

Subjects will not be allowed to apply moisturizing creams or oils to the dosing site within 1 hour prior to dosing, or to the assessment site within 1 hour prior to the capsaicin-evoked pain test.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- vital signs
- blood samples
- cardiac monitoring/ECG extractions
- any other procedures.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, PK analysis will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the

event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Pharmacodynamic Assessments

Capsaicin intradermal test will be performed for subjects in Groups A2, A4, and A6. Each subject will be tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).

7.2.1. Capsaicin-evoked Pain Model

The capsaicin model will be conducted by intradermal injection of capsaicin (100 µg in 100 µL of sterile saline containing 8% [w/w] Tween 80) into the skin of the anterior aspect of the forearm, midway between the elbow and the wrist. The bleb area (wheal) will be a sign of local plasma extravasation. An assessment of the pain intensity related to capsaicin injection will be estimated by repeated use of a VAS from injection to 5 minutes post-injection or until the pain intensity returned to zero. The AUC, E_{max}, and tE_{max} will be calculated and reported using dedicated software.

7.2.2. Secondary Hyperalgesia

The area of secondary hyperalgesia will be quantified with a 60-g weighted von Frey hair, by stimulating along 8 linear paths (4 vectors crossing at the location of the injection site) arranged vertically and horizontally around the stimulation site in 5-mm steps (starting approximately 6 cm away from the injection site). The area of secondary hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection.

7.3. Safety and Tolerability Assessments

Safety and tolerability assessments will be conducted at the times indicated in the Schedule of Assessments (Appendix 6). Timepoints may be adjusted based on an ongoing review of the data, and additional assessments may be conducted if deemed necessary by the Investigator or designee.

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked

about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a follicle-stimulating hormone (FSH) test and pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

Subjects must be supine for at least 5 minutes before blood pressure, pulse rate, and respiratory rate measurements.

7.3.4. Electrocardiogram

7.3.4.1. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value > 500 msec
- QTcF change from the mean baseline (Day 1 predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.4.2. Continuous (24-hour) Electrocardiogram

At the times indicated in the Schedule of Assessments (Appendix 6), continuous (24-hour) ECGs will be performed.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint. Each extraction will last for 5 minutes. Environmental distractions (eg, television, playing games, radio, conversation) should be avoided during the pre-ECG time window.

Continuous 24-hour ECGs are not planned for Part B of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.3.5. Heat Pain Threshold Test

Heat pain threshold tests will be conducted at the times indicated in the Schedule of Assessments (Appendix 6).

A computer-controlled thermal sensory analyzer device will be used to measure the heat pain threshold and tolerance level of the subjects. The heat pain assessments will be conducted on the subject's thigh.

Heat Pain Threshold:

For heat pain threshold measurements, the thermode will be placed directly on the skin of the right thigh, within an area selected before the start of the experiment and defined by surgical marking. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in

their dominant hand, to indicate when the heat pain threshold (first sensation of heat pain) is reached by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Heat Pain Tolerance:

For heat pain tolerance measurements, the thermode will be placed within the same surgically marked skin area of the anterior side of the right thigh, which was used to assess heat pain threshold. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in their dominant hand, to indicate when the heat-evoked pain has reached an intensity that is no longer tolerable, by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Safety Precautions

As there is a risk that OLP-1002 may affect the heat pain threshold, Covance CRU will put appropriate safety measures in place to ensure that subjects are not exposed to extremes of temperature when taking a shower or consuming hot drinks. During the heat pain safety assessments, the cut-off temperature for either test is 53 °C in order to prevent skin injury.

7.3.6. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

7.3.7. Body Weight and Height

Body weight (in underclothes) and height will be recorded at the times indicated in the Schedule of Assessments in Appendix 6. BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{body weight (kg)}}{(\text{height [m]})^2} \quad (\text{kg/m}^2)$$

7.3.8. Injection Site Assessments

Injection site assessments will be made at the times indicated in the Study Plan (Appendix 6).

Assessments will involve evaluation of the dosing site for the following criteria:

- Pain will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Requires medical intervention greater than analgesia

• Redness will be assessed by estimating the size of the red patch at the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm	51-100 mm	More than 100 mm	Requires medical intervention greater than analgesia

• Swelling will be assessed by estimating the size of the raised area around the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm and does not interfere with activity	51-100 mm or interferes with activity	More than 100 mm and prevents daily activity	Requires medical intervention greater than analgesia

In addition, how the swelling affects the subject in their daily routing activities will be considered.

• Tenderness will be evaluated using the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Mild pain to touch	Moderate Pain to touch	Severe pain to touch	Requires medical intervention greater than analgesia

- Bruising and ulceration will be evaluated as being present or absent.

Local tolerability ratings of ≥Grade 3 and the presence of ulceration will be recorded as an adverse event.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. In order to achieve PD endpoints in Part A, additional subjects will be included in 3 groups (8 subjects in total; 6 active: 2 placebo). Up to 3 additional groups may be added to Part A, consisting of either 4 subjects (3 active; 1 placebo) or 8 subjects (6 active; 2 placebo). Up to 3 additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.2. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of

OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

8.4. Pharmacodynamic Analyses

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned.

8.5. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- Mild: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but posing no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- Not Related: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- Unlikely Related: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- Related: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at the Follow-up visit will be followed up, where possible,

until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit (CRU). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Covance Drug Safety Services (DSS) Europe, Maidenhead, UK are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to DSS and the Sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Covance DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 2 working days of the initial notification to DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy reported by female subjects or

the female partners of male subjects should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total protein Urea	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[a]:	**Drug screen[b]:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test MDMA Alcohol breath test	Follicle-stimulating hormone[a] Serum pregnancy test (human chorionic gonadotropin)[a] Urine pregnancy test[c]

[a] Only analyzed at Screening.
[b] Only analyzed at Screening and Check-in.
[c] A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	19	76
Clinical laboratory evaluations (excluding serology)	7.5	6	45
Serology	3.5	1	3.5
Total:			124.5

Part B

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	29	116
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			194.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject during the study will not exceed that donated during a standard blood donation (approximately 500 mL).

Appendix 4: Contraception Guidance

Definitions

Females of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Females of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary (non-barrier) methods of contraception include:

- hormone injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
    - bilateral tubal ligation
    - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)

- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects can only choose a cervical cap or diaphragm if they have already had a prescription and fitting by their healthcare provider to ensure protocol requirements are met. Female subjects of childbearing potential should refrain from donation of ova from Check-in until 90 days after the Follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide
- vasectomised male subject (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success).

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the Follow-up visit.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the Follow-up visit.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a

public registry, all identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled and randomized subject, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

Study Plan – Part A (Single Dose)

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Urine drugs of abuse screen		X	X							
Alcohol breath test		X	X							
Cotinine test		X	X							
Serology		X								
FSH and serum pregnancy test[a]		X								
Urine pregnancy test[a]			X							X
Informed consent	X	X								
Study residency:										
Check-in			X							
Check-out					Day 3 (48 hours postdose)					
Non-residential visit	X	X				X	X	X	X	X
Study drug administration:					Day 1 (0 hours)					
Safety and tolerability:										
Adverse event recording		X	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording		X	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature		X			Predose, 1, 2, 4, 8, 24 (± 1 hour), and 48 hours postdose	X	X	X	X	X

	Pre-screening[d]	**Screening**	**Day -2**	**Day -1**	**Days 1 to 3**	**Day 4**	**Day 7 (± 2 days)**	**Day 10 (± 2 days)**	**Day 14 (± 2 days)**	**Poststudy (Day 28 ± 2 days)**
Supine 12-lead ECG		X			Predose, 4, 24 (± 1 hour) and 48 hours postdose		X		X	X
Continuous ECG extraction[b,c]				-24, -23.5, -23, -22.5, -22, -21.5, -21, -20, -18, -16, -12 hours	Day 1: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours					
Heat pain threshold test (heat pain threshold and heat pain tolerance)					Day 1: predose, 2, 4, 12, and 24 hours postdose (± 1 hour)					
Clinical chemistry, haematology, and urinalysis		X	X		48 hours postdose		X		X	X
Height and BMI		X								
Body weight		X	X							X
Physical examination		X								
Symptom-directed physical examination					Prior to discharge		X		X	X

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Injection site assessment					Predose, 1, 2, 4, 8, 24, 48 hours postdose		X		X	X
Pharmacokinetics[e]										
Blood sampling					Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose	X	X	X	X	X
Pharmacodynamics[d]:										
Intradermal capsaicin test (capsaicin-evoked pain and secondary hyperalgesia measurement)	X		X		Day 2 (The area of secondary area of hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection)					

Abbreviations: BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone.
[a] Female subjects only; a positive urine pregnancy test result will be confirmed with a serum pregnancy test.
[b] All times are relative to dosing with OLP-1002.
[c] Continuous ECG recording may begin at approximately 25 hours before dosing to allow for checks to be completed prior to the first extraction timepoint and will continue for 24 hours postdose, ie, until after the last timepoint for ECG extraction (24 hours postdose). At timepoints for ECG extractions, subjects will be supinely resting for a total of 15 minutes (10-minute supine rest period, 5-minute extraction). Data will be archived for potential future analysis and will not be available for review during the study.
[d] Pharmacodynamic assessment groups only.
[e] PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

Study Plan – Part B (Multiple Dose)

	Screening	Day -1	Days 1-15	Day 18 (± 2 days)	Day 22 (± 2 days)	Day 25 (± 2 days)	Day 29 (± 2 days)	Poststudy (Day 57 ± 2 days)
Inclusion/exclusion criteria	X							
Demographic data	X							
Medical history	X							
Urine drugs of abuse screen	X	X						
Alcohol breath test	X	X						
Cotinine test	X	X						
Serology	X							
FSH and serum pregnancy test[a]	X							
Urine pregnancy test[a]		X			X		X	X
Informed consent	X							
Study residency:								
Check-in		X						
Check-out			Day 15 (48 hours postdose)					
Non-residential visit	X			X	X	X	X	X
Study drug administration:			Days 1, 4, 7, 10, and 13					
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording	X	X	Ongoing	X	X	X	X	X

Supine blood pressure, pulse rate, respiratory rate, and body temperature	X		Day 1: predose, 1, 2, 4 and 8 hours postdose Day 2, Day 4 (postdose), Day 5, Day 7 (postdose), Day 9, Day 10 (postdose), Day 12, Day 13: predose, 1, 2, 4 and 8 hours postdose, and Day 15	X	X	X	X	X
	Screening	**Day -1**	**Days 1-15**	**Day 18**	**Day 22**	**Day 25**	**Day 29**	**Poststudy (Day 57 ± 2 days)**
Heat pain threshold test (heat pain threshold and heat pain tolerance)	X		Day 1 and Day 13: predose, 1, 2, 4, 8, 24 hours postdose					
Supine 12-lead ECG	X		Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Clinical chemistry, haematology, and urinalysis	X	X	Days 2, 5, 9, 12, 17		X		X	X
Height and BMI	X							
Body weight	X	X						X
Physical examination	X							
Symptom-directed physical examination			Days 1, 4, 7, 10, 13		X		X	X
Injection site assessment			Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X

Pharmacokinetics:								
Blood sampling[b]			Day 1 and Day 13: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose Days 4, 7, 10 Predose Day 15	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone.
[a] Female subjects only; a positive urine pregnancy test results will be confirmed with a serum pregnancy test.
[b] PK timepoints will be reviewed based on emerging data and may be updated.

Appendix 7: Protocol Amendment Summary of Changes

Protocol Amendment 4 (Version 3; 29 January 2019)

This substantial amendment has been issued to update the female contraception criteria to allow female subjects to use alternative forms of contraception including the combined oral contraceptive pill, combined hormonal patch, and combined hormonal vaginal ring. Additionally, it has been clarified that only a serum pregnancy test will be conducted at Screening.

A detailed summary of changes is presented below. For each section, deleted text is shown in s~~trikethrough~~, and new text is shown in **bold**:

Appendix 4

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary ~~highly effective~~ and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary ~~highly effective~~ **(non-barrier)** methods of contraception include:

- **hormone injection (as prescribed)**
- **combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)**
- **combined hormonal patch (as prescribed)**
- **combined hormonal vaginal ring (as prescribed)**
- surgical method performed at least 3 months prior to the Screening visit:
    - bilateral tubal ligation
    - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)
- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Appendix 6

~~Hormone panel~~ was replaced by **FSH and serum pregnancy test** in the study plan for Part A and Part B for clarity.

A footnote was added to the study plan for Part A and Part B to specify that the FSH and serum pregnancy test will be conducted for female subjects only.

Urine pregnancy test at Screening removed for Part A and Part B.

Protocol Amendment 3 (Version 2.2; 12 December 2018)

This non-substantial amendment has been issued to include a clinical laboratory assessment on Day -2 in Part A.

Appendix 3

Additional clinical laboratory sample added to Part A. Total blood volume withdrawn in Part A updated to 124.5 mL.

Appendix 6 Study Plan (Part A)

Clinical chemistry, haematology, and urinalysis assessment added on Day -2.

Protocol Amendment 2 (Version 2.1; 29 November 2018)

This non-substantial amendment has been issued to correct minor inconsistencies in PK sampling timepoints, data cut off for dose escalation, clinical laboratory assessment timepoints, and the synopsis. Additionally, details of the injection site assessments have been added to the protocol.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Synopsis: Endpoints

Text added:

Safety:
Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, **heat pain threshold and tolerance,** and physical examinations.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from groups that received lower doses of OLP-1002.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day **10** (**216** hours postdose) from groups that received lower doses of OLP-1002.

Section 7.3.8

Entire section added to describe injection site assessments.

Appendix 3

Total blood volume for PK analysis (76 mL) added.

Appendix 6 - Schedule of assessments Part A

24 hour postdose continuous ECG recording timepoint added.

Appendix 6 - Schedule of assessments Part B

Clinical chemistry, haematology, and urinalysis for Days 1-15 previously read:

Days 2, ~~4~~, ~~7~~, ~~10~~,~~13~~

Clinical chemistry, haematology, and urinalysis for Days 1-15 now reads:

Days 2**, 5, 9, 12, 17**

PK blood sampling for Days 1-15 previously read:

Day 1 and Day ~~15~~: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, ~~8,~~ ~~11, 15~~ Predose

PK blood sampling for Days 1-15 now reads:

Day 1 and Day **13**: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, **7, 10** Predose
Day 15

Protocol Amendment 1 (Version 2; 02 October 2018)

This amendment has been generated following the non-acceptance of the original protocol (version 1) by the Medicines and Healthcare products Regulatory Agency (MHRA) on 20 September 2018. All changes made have been in response to comments provided by the MHRA.

The primary changes in this amendment are:

1. Inclusion of PK sampling in Parts A and B:
    - PK objective and exploratory endpoints added (Section 2).
    - Discussion of PK included Section 3.4.
    - PK stopping criteria added to Section 3.7.
    - PK assessments included in Section 7.1.

- PK population and analysis (Section 8.2.1).
- Blood volumes updated to include samples for PK assessments (Appendix 3).

2. Exclusion and stopping criteria updated
    - Women who are pregnant or breastfeeding have been excluded from the study (Section 4.2).
    - Liver function tests, tachycardia, and hypertension stopping criteria have been updated (Section 3.7 and Section 4.4).
    - Stopping criteria for SAEs and serious AEs have been added (Section 3.7 and Section 4.4).
3. Safety, tolerability, and PK data up to Day 22 in Part B will be reviewed prior to dose escalation (Section 3.1.2).
4. Sentinel dosing included in Part B (Section 3.1.2).
5. It has been specified that the maximum dose for additional groups will not exceed 20 µg (Section 3.5.3).

Minor changes:

1. Additional clinical laboratory evaluations have been included on Day 14 in Part A.
2. The definition of the Safety population has been updated to include all subjects who receive OLP-1002.
3. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Section 1.6

Previously read:

This information, together with the pharmacodynamic (PD data, will help establish the doses and dosing regimen suitable for future studies in patients.

Now reads:

This information, together with the pharmacodynamic (PD) **and pharmacokinetic (PK)** data, will help establish the doses and dosing regimen suitable for future studies in patients.

Section 2.1

Objective added:

Where possible, single and/or multiple subcutaneous dose pharmacokinetics of

OLP-1002 in healthy subjects will be determined.

Section 2.2.1

Endpoint added:

- **demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.**

Section 2.2.2

Endpoints added:

- **For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])**
  - **AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)**
  - **maximum observed plasma concentration (C_{max}) (actual and DN)**

  Secondary PK

  - **time of the maximum observed plasma concentration (t_{max})**
  - **apparent plasma terminal elimination half-life ($t_{1/2}$)**

- **For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)**
  - **$AUC_{0-\infty}$ (actual and DN)**
  - **C_{max} (actual and DN)**

  Secondary PK

  - **minimum observed plasma concentration (C_{min})**
  - **t_{max}**
  - **$t_{1/2}$**
  - **observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)**
  - **observed accumulation ratio based on C_{max} (RAC_{max}).**
  - **Temporal change parameter (TCP)**

Other PK parameters may also be added if deemed necessary.

Section 3.1.1

Previously read:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from the lower dose levels.

Now reads:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, **PK,** and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day **10** (**216** hours postdose) from the lower dose levels. **For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to**

dose escalation.

Figure 1 – footnote

Text added:

Groups A9 to A11 may be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Figure 2 – footnote

Text added:

Groups B4 to B6 will be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Section 3.1.2

Previously read:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. ~~There will be no sentinel dosing in Part B.~~ For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from the lower dose levels. Part B may start after a review of the safety ~~and~~ tolerability for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Now reads:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses

1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from the lower dose levels. Part B may start after a review of the safety**,** tolerability**, and available PK data** for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Section 3.3

Previously read:

Following review of the safety, tolerability, and PD data, additional dose groups may be added to the study.

Now reads:

Following review of the safety, tolerability, **PK,** and PD data **(where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7])**, additional dose groups may be added to the study. **The maximum dose for any additional group will not exceed 20 µg.**

Section 3.4

Previously read:

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

~~Pharmacokinetic analysis will not be conducted in this study.~~ The bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of

5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose~~s~~ would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. ~~Thus, the additional burden of sampling procedures would not be justified by the quality of the data which it would generate.~~

Now reads:

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased

sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. **Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable.** It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. **In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.**

Section 3.4.1

Previously read:

In Part B, ~~all subjects in a group will be dosed on the same day~~. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3).

Now reads:

In Part B, **sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day**. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). **If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.**

Section 3.5.3

Text added:

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not

exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of ~~5~~ subjects, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002. **For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.**

In Part B, doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. **Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.**

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of **3 or 4** subjects**, respectively**, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Section 3.7

Previously read:

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in ~~liver function tests~~ ~~(~~aspartate aminotransferase, alanine aminotransferase~~,~~ alkaline phosphatase ~~and total bilirubin)~~ defined as 3 times the upper limit of normal in ~~3~~ or more subjects in a group ~~(~~confirmed with repeat testing~~)~~.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.

Now reads:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- **One or more subjects experience an SAE that is considered to be related to OLP-1002.**
- **Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.**
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase **or** alkaline phosphatase **(**defined as 3 times the upper limit of normal**), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be** confirmed with repeat testing.

- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- **The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).**

Section 4.2

Exclusion criteria added:

4. Female subjects who are pregnant or breastfeeding.

Section 4.4

Previously read:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal

Now reads:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal**, including:**
  - **a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),**
  - **severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),**
  - **elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),**
  - **QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),**
  - **Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),**

- **Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).**

Section 7.1

Section added:

7.1 Pharmacokinetic Assessments

7.1.1 Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, only samples collected from subjects that received >12 µg OLP-1002 will be initially analyzed. If PK data is quantifiable at concentrations of OLP-1002 >12 µg, samples from lower dose groups will be retrospectively analyzed. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2 Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

Section 8.2

Previously read:

8.2.~~1~~ Pharmacodynamic population

The PD population will include all subjects who received at least 1 dose of ~~study treatment~~ OLP-1002 or placebo and for whom PD can be evaluated.

8.2.~~2~~ Safety Population
The safety population will include all subjects who received at least 1 dose of ~~study treatment~~ or placebo ~~and have at least 1 postdose safety assessment~~.

Now reads:

8.2.1 Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.**2** Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.**3** Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3 Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma and urine concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

Appendix 3

Table updated:

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis*	**4**	**19**	**76**
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			~~33.5~~**109.5**

Part B

	Volume per blood sample (mL)	**Maximum number of blood samples**	**Total amount of blood (mL)**
Pharmacokinetic analysis	**4**	**29**	**116**

Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			~~78.5~~**194.5**

Appendix 6

PK and Blood sampling rows added to the schedule of events for Part A and Part B. In the Schedule of events for Part A, footnote e was added. In the Schedule of events for Part B, footnote b was added.

Clinical chemistry, hematology, and urinalysis was added to the Schedule of events for Part A on Day 14.

Protocol

OLP-1002 – A First-in-human, Double-blind, Placebo-controlled, Single and Multiple Subcutaneous Dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Male and Female Subjects

Protocol Status: Final
Protocol Date: 12 December 2018
Protocol Version: 2.2

Investigational Product: OLP-1002

Protocol Reference Number: OLP-1002-001
Covance Study Number: 8379789
EudraCT Number: 2018-003085-13

Sponsor:
OliPass Corporation
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Study Site:
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United Kingdom

Sponsor Signatory:
[redacted]

Principal Investigator:
[redacted]

SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

December 13, 2018

[redacted]

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

[redacted]

[redacted]
Principal Investigator

13 DEC 2018
Date

STUDY IDENTIFICATION

Sponsor	OliPass Corporation Ace Dongbaek Tower 20th Floor 16 Beon-gil, 16-4 Dongbaek Jungang-ro Giheung, Yongin, Gyeonggi 17015 Republic of Korea
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Sponsor's Medical Contact	[redacted] OliPass Corporation Ace Dongbaek Tower 20th Floor 16 Beon-gil, 16-4 Dongbaek Jungang-ro Giheung, Yongin, Gyeonggi 17015 Republic of Korea
Medical Monitor (24-hour emergency medical contact)	[redacted]
Study Site	Covance Clinical Research Unit Ltd. Springfield House, Hyde Street, Leeds, LS2 9LH United Kingdom
Principal Investigator	[redacted] Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH United Kingdom [redacted]
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	[redacted]
Clinical Laboratory	[redacted]
Statistician	[redacted] Covance

SYNOPSIS

Title of study: OLP-1002 – A first-in-human, double-blind, placebo-controlled, single and multiple subcutaneous dose, safety, tolerability, pharmacokinetic, and pharmacodynamic study in healthy male and female subjects
Objectives: The primary objective of the study is to assess the safety and tolerability of single and multiple subcutaneous doses of OLP-1002 in healthy subjects. The exploratory objectives of the study are to evaluate the pharmacodynamic effect of OLP-1002 following single subcutaneous doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of a single subcutaneous doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.
Study design: This will be a double-blind, randomized, placebo-controlled, single and multiple subcutaneous dose study conducted in 2 parts, including healthy male and female subjects.
Number of subjects: Part A: 44 subjects will be studied in 8 groups (5 groups of 4 and 3 groups of 8). Part B: 24 subjects will be studied in 3 groups (Groups B1 to B3). Up to 24 additional subjects may be recruited into Part A and Part B of the study if required.
Diagnosis and main criteria for inclusion: Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 28.0 kg/m^2 (inclusive).
Investigational products, dose, and mode of administration: Test product: OLP-1002 Proposed dose levels for Part A: 30 ng, 120 ng, 400 ng, 1.2 µg, 3 µg, 6 µg, 12 µg, and 20 µg. Proposed dose levels for Part B: the doses for Part B will be decided in consultation with the Sponsor and on the basis of data from Part A of the study. The highest dose in Part B will be up to 50% of the highest dose in Part A. Administration route: subcutaneous
Reference product and mode of administration: Reference product: placebo Administration route: subcutaneous
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to Follow-up): approximately 8 weeks for Part A and approximately 12 weeks for Part B.

Endpoints:

Pharmacodynamics:

In Part A, the analgesic effect of OLP-1002 will be investigated in 3 groups consisting of 8 subjects (6 active: 2 placebo) using experimental capsaicin-evoked pain methods. Measurement of capsaicin-evoked pain will be performed at pre-screening, baseline and on Day 2, and secondary hyperalgesia at 5 and 30 minutes post-capsaicin injection. Continuous electrocardiogram (ECG) recording will be conducted to investigate the effect of OLP-1002 on cardiac function.

Safety:

Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, heat pain threshold and tolerance, and physical examinations.

Pharmacokinetics:

In Part A, the following PK parameters will be determined where possible: area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$), maximum observed plasma concentration (C_{max}), time of the maximum observed plasma concentration (t_{max}), and apparent plasma terminal elimination half-life ($t_{1/2}$). PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

In Part B, the following PK parameters will be determined where possible: AUC over a dosing interval ($AUC_{0-\tau}$), $AUC_{0-\infty}$, $C_{max,}$ minimum observed plasma concentration (C_{min}), t_{max}, $t_{1/2}$, observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$), observed accumulation ratio based on C_{max} (RAC_{max}), and Temporal change parameter (TCP). PK samples from all groups in Part B will be analyzed.

Statistical methods:

Pharmacodynamics:

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of pharmacodynamic data is planned.

Safety:

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

Pharmacokinetics:

Individual plasma concentrations and PK parameters of OLP-1002 will be listed and summarized using descriptive statistics. Individual and mean OLP-1002 concentration-time profiles will be presented graphically.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours postdose
BMI	body mass index
C_{max}	maximum observed plasma concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSA	clinical study agreement
DN	Dose normalized
DRG	dorsal root ganglion
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
E_{max}	maximum pain intensity
FCA	Freund's Complete Adjuvant
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia’s method
SAE	serious adverse event
SC	subcutaneous(ly)
SNL	spinal nerve ligation
$t_{1/2}$	elimination half-life
tE_{max}	time of maximum pain intensity
T_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
VAS	Visual Analogic Scale
VGSC	voltage-gated sodium channel

1. INTRODUCTION

1.1. Overview

OLP-1002 is a novel peptide nucleic acid (PNA) derivative which acts as a specific voltage-gated sodium channel (VGSC) protein ($Na_v1.7$) inhibitor, and is being developed by OliPass for the treatment of pain.

The $Na_v1.7$ protein is a subtype of VGSCs. $Na_v1.7$ is particularly important in nociception and pain signaling, with congenital loss-of-function mutations in $Na_v1.7$ resulting in the inability to experience pain. Selective $Na_v1.7$ inhibitors are believed to have the potential to treat severe pain safely[1]. The active sites of VGSC subtypes are virtually indistinguishable by their 3-dimensional structure and thus the discovery of selective $Na_v1.7$ small molecule inhibitors has been extremely challenging. Since inhibition of $Na_v1.5$ subtype elicits long QT cardiotoxicity, inhibition of $Na_v1.5$ subtype should be avoided at therapeutic doses.

To date, there are several $Na_v1.7$ inhibitors claimed to be selective that have been evaluated in human subjects:

- Vixotrigine (formerly known as raxatrigine) inhibits $Na_v1.7$ as well as other VGSC subtypes. Vixotrigine is in phase III clinical development for trigeminal neuralgia. Due to the limited $Na_v1.7$ selectivity over $Na_v1.5$, vixotrigine was evaluated primarily in patients with a low heart risk.
- Funapide is a $Na_v1.7$ inhibitor with limited $Na_v1.7$ selectivity, and was in phase IIb clinical trials as of July 2014. Although funapide showed analgesic activity in a small number of erythromelalgia patients, dose-limiting adverse events (AEs), including dizziness and somnolence, were observed[2]. The central nervous system (CNS) AEs were due to its poor $Na_v1.7$ selectivity.
- PF-05089771 is a $Na_v1.7$ selective inhibitor with a claimed $Na_v1.7$ selectivity of > 2000-fold versus other subtypes of sodium channel and was evaluated in patients of erythromelalgia or dental pain. It is thought low drug concentrations achieved in the target tissue could be a possible explanation for its poor analgesic activity in human patients[3].

OLP-1002 is fully complementary to a 14-mer RNA sequence spanning the junction of intron 4 and exon 5 in the human SCN9A pre-mRNA which codes for the $Na_v1.7$ channel. OLP-1002 yields SCN9A mRNA splice variant(s) encoding variant $Na_v1.7$ protein(s) lacking the sodium channel activity (ie, a non-functional channel), thereby inhibiting $Na_v1.7$ channel function.

1.2. Summary of Nonclinical Pharmacology

1.2.1. In Vitro Pharmacology Studies

Overall, results from the in vitro pharmacology studies showed OLP-1002 elicits responses consistent with its designed function[4]. It inhibits SCN9A mRNA expression and yields the

$Na_v1.7$ variant protein or proteins lacking sodium channel activity. Its effects are highly selective, which may provide for an improved margin of safety compared to other $Na_v1.7$ inhibitors.

OLP-1002 at 1 to 100 zM in PC3 prostate carcinoma cells induced exon skipping and yielded SCN9A mRNA splice variant(s) encoding a $Na_v1.7$ variant protein or proteins lacking sodium channel activity.

In rat dorsal root ganglion (DRG) neuronal cells, OLP-1002 at 1000 zM inhibited $Na_v1.7$ protein expression by > 50%, while OLP-1002R at 100 and 1000 zM inhibited $Na_v1.7$ expression almost completely. As OLP-1002R is fully complementary to rat SCN9A pre-mRNA, OLP-1002R would be predicted to be more potent than OLP-1002 in this cell type.

SCN9A mRNA expression level was evaluated by quantitative polymerase chain reaction (qPCR). OLP-1002 inhibited the expression of the SCN9A mRNA in PC3 cells with sub-attomolar potency.

In SH-SY5Y human neuroblastoma cells stimulated with tumor necrosis factor (TNF)-1α to upregulate the expression of SCN9A mRNA, OLP-1002 decreased expression by 46% to 49% at 1 fM to 10 pM. In rat DRG neuronal cells, OLP-1002 at 1 fM significantly decreased SCN9A mRNA expression by 54%.

In rat DRG neuronal cells, OLP-1002 markedly and significantly inhibited the sodium current by 77% at 0.1 aM and 73% at 1 aM, while for OLP-1002R, the inhibition was 66% at 0.1 aM and 70% at 1 aM. Given that rat DRG neuronal cells express various subtypes of sodium channel, the observed inhibitions of 66% to 77% correspond to the complete knockout of the $Na_v1.7$ sodium channel subtype with OLP-1002 or OLP-1002R.

The $Na_v1.7$ selectivity over $Na_v1.5$ was evaluated in H9C2 rat cardiomyocytes which are known to abundantly express the rat $Na_v1.5$ sodium channel subtype. Following incubation with OLP-1002 or OLP-1002R at 1 aM or 1 pM, there were no notable decreases in the sodium current. Considering that OLP-1002 and OLP-1002R inhibit the expression of $Na_v1.7$ protein at 1 aM or lower in rat DRG neuronal cells, the $Na_v1.7$ selectivity of OLP-1002 and OLP-1002R over $Na_v1.5$ is estimated to be in excess of one million-fold. Such a large $Na_v1.7$ selectivity over $Na_v1.5$ has not been realized with small molecule $Na_v1.7$ inhibitors, suggesting that OLP-1002 potentially offers pain management with much greater cardiovascular safety.

1.2.2. In Vivo Pharmacology Studies

Spinal nerve ligation (SNL) has been widely applied as a rat model for neuropathic pain. OLP-1002 and OLP-1002R were found to be very potent, but highly variable in potency, in reversing neuropathic allodynia in this model. Analyses of the therapeutic potency strongly suggested that a marked proportion of subcutaneously (SC) administered OLP-1002 or OLP-1002R may have been topically delivered directly to the spinal nerves exposed in the dorsal cavity created during the SNL modelling. In addition, the variability of the therapeutic potency may be due to a variable degree of healing of the SNL surgery wound. If an animal

recovers slowly, the animal tends to be left with a dorsal cavity. Therefore, estimations of potency in these studies with this model should be treated with caution.

In one study using the SNL model, allodynia in rats was slowly and gradually reversed by OLP-1002 SC administered at nominal doses of 1, 3, and 6 pmol/kg once every 2 days (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). As the onset time for pain reduction was 4 days, the doses used were not sufficient for fast onset of activity. In this study, the animals should have reasonably recovered from the dorsal wound, and therefore less susceptible to topical delivery directly to the exposed spinal nerves. However, in another study in this model, when OLP-1002 was intraperitoneally (IP) administered once every 3 days to avoid the likelihood of local delivery to the spinal nerves, OLP-1002 surprisingly reversed the allodynia at 5 fmol/kg, and was superior or comparable to pregabalin 30 mg/kg, a gold standard for neuropathic pain studies. The high potency shown at 5 fmol/kg IP strongly suggests the possibility that OLP-1002 is efficiently absorbed by the enteric nervous system, travels to the spinal cord, and then redistributes to the spinal nerves of the SNL ligation. This opens the possibility of efficient oral delivery of OLP-1002 to the spinal cord.

When evaluated for their ability to reverse the inflammatory pain in rats inflicted with Freund's Complete Adjuvant (FCA)-induced severe paw inflammation, OLP-1002 at 300 pmol/kg and OLP-1002R at 100 pmol/kg significantly reversed the thermal hyperalgesia, and both were more effective than pregabalin 30 mg/kg.

Paw burn injury induces hyperalgesia in rats and is known to upregulate $Na_v1.7$ expression in the L5 and L6 DRGs of the affected side. Burn injury induces a far weaker degree of paw inflammation than FCA-induced paw inflammation. OLP-1002 SC administered inhibited the thermal hyperalgesia in paw burn injury in a dose-dependent manner. At 25 fmol/kg, OLP-1002 did not inhibit thermal hyperalgesia. Although OLP-1002 at 625 fmol/kg significantly inhibited the thermal hyperalgesia, the efficacy was moderate and weaker than pregabalin 30 mg/kg. This suggests that SC dosing does not offer the local topical delivery to spinal nerves in this model as seen in rats without a dorsal cavity wound. In this study, the $Na_v1.7$ expression in the DRG of the burn injury side significantly decreased by 58% with 625 fmol/kg OLP-1002, validating the target engagement for analgesic activity.

An intraplantar injection of formalin induces severe acute pain. The contributors to acute pain are known to be complex and require further elucidation. However, acute peripheral inflammation is known to contribute much to Phase II Pain (pain from 10 to 40 min after the formalin injection). In this model, OLP-1002 significantly inhibited Phase II Pain at comparable or saturated efficacy when SC administered at 10 to 100 pmol/kg (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). Thus peripheral acute inflammatory pain could be treated with 10 pmol/kg or less.

1.2.3. Ex Vivo Pharmacology Studies

One day post-SC injection, OLP-1002 and OLP-1002R at 100 pmol/kg significantly inhibited the expression of $Na_v1.7$ protein by 39% and 57%, respectively, in the spinal cord of rats subjected to SNL.

In other rats subjected to SNL, OLP-1002R slowly and gradually reversed the allodynia in a dose-dependent manner. OLP-1002R at 30 fmol/kg (the highest dose administered) had the greatest effect, but the dose was not high enough to elicit full therapeutic efficacy. OLP-1002R inhibited expression of $Na_v1.7$ protein in these animals, most notably at 1 fmol/kg, and decreased SCN9A mRNA expression by approximately 40% at 1 to 30 fmol/kg. The observed inhibitions were largely consistent with the in vivo therapeutic activity findings.

Taking all the in vivo and ex vivo findings together, OLP-1002R was concluded to inhibit neuropathic allodynia by inhibiting the expression of the SCN9A mRNA and the $Na_v1.7$ protein.

1.3. Summary of Safety Pharmacology

In vitro, OLP-1002 did not inhibit the human ether-à-go-go-related gene (hERG) channel current expressed in human embryonic kidney (HEK) cells at the highest concentration tested 2 μM (the limit of the validated analytical method for OLP-1002).

In the in vivo safety pharmacology studies, OLP-1002 SC administered at dose levels up to 100 nmol/kg had no effect on body temperature, neurological function, or respiratory function in rats, and had no significant toxic effect on cardiovascular function in cynomolgus monkeys.

1.4. Summary of Toxicology

In rats, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included pigment accumulation in the kidney of males administered 100 nmol/kg/dose and females administered ≥ 10 nmol/kg/dose, foreign material and vacuolated macrophage infiltrates in males and/or females administered ≥ 1 nmol/kg/dose, and an increased incidence and/or severity of mononuclear cell infiltrates at the injection sites in males and/or females administered ≥ 10 nmol/kg/dose. These findings persisted through the recovery phase in animals administered 100 nmol/kg/dose. However, the effects were considered non-adverse due to their mild severity and lack of impact on animal health and wellbeing. The no-observed-adverse-effect level (NOAEL) was 100 nmol/kg/dose. This dose level corresponded to maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from 0 to 24 hours postdose (AUC_{0-24}) values of 27.6 ng/mL and 174 ng·hr/mL, respectively, in males and 24.9 ng/mL and 128 ng·hr/mL, respectively, in females on Day 88 of the dosing phase.

In cynomolgus monkeys, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included mononuclear cell infiltrates at the SC injection sites of animals administered ≥ 10 nmol/kg/dose. This finding was not resolved with the completion of the recovery phase. However, the effects of 100 nmol/kg/dose were considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing. The NOAEL was 100 nmol/kg/dose (equivalent to 462.29 μg/kg/dose), which corresponded to C_{max} and AUC from 0 to 72 hours postdose (AUC_{0-72}) values of 121 ng/mL and 2840 ng·hr/mL in males, respectively, and 216 ng/mL and 4840 ng·hr/mL in females, respectively, on Day 88 of the dosing phase.

The genotoxic and mutagenic potential of OLP-1002 was evaluated with standard Good Laboratory Practice (GLP) via in vitro bacterial mutagenicity and chromosomal aberration studies, and was found to be negative.

1.5. Summary of Nonclinical Pharmacokinetics

In rats, following a single SC dose of ^{14}C-OLP-1002, the time of maximum observed concentration (T_{max}) was 0.5 to 1 hour for both radioactivity and parent compound. Plasma concentrations of total radioactivity were quantifiable through the last sampling time of 72 hours postdose, but was variable for the parent compound. The elimination half-life ($t_{1/2}$) of total radioactivity from plasma was 23 hours. Total radioactivity distributed into tissues, including those of the CNS protected by the blood-brain barrier. ^{14}C-OLP-1002-derived total radioactivity was not rapidly excreted from rats, with minimal amounts present in urine and feces. The bulk of the total radioactivity remained in carcasses, primarily in kidneys (cortex and medulla) and liver. Parent ^{14}C-OLP-1002 was present in plasma and tissues, but concentrations declined over time and were substantially lower than total radioactivity concentrations at the later sampling times.

After a single SC administration of ^{14}C-OLP-1002 to rats, the highest concentrations of total radioactivity were retained predominantly in the liver (10.4% to 13.3% of the dose), kidney cortex (3.47% to 4.96%), and kidney medulla (1.10% to 1.59% of the dose) through 168 hours postdose. For all other tissues, the total amounts of total radioactivity were substantially less, ranging from 0.0000203% in the 5th DRG to 0.327% in the spleen. Radioactivity was excreted slowly via both the renal and fecal routes of elimination. Total average recoveries of radioactivity in urine and feces through 336 hours postdose accounted for 2.31% and 1.75% of the administered radioactivity, respectively. The bulk of the administered total radioactivity was retained in the rat carcasses through 168, 336, 504, and 840 hours postdose. The kidney cortex, kidney medulla, and liver were the 3 tissues that retained the greatest amounts of the administered radioactivity.

Following a 16.1-µg/kg dose in rats, the plasma concentrations were still quantifiable at 72 hours postdose and the rate of elimination was slow, with $t_{1/2}$ 17.5 hours. It was not possible to accurately define the elimination phase for the 2.67- and 5.28-µg/kg dose levels.

In cynomolgus monkeys, following a single SC dose of ^{14}C-OLP-1002, T_{max} ranged from 0.25 to 1 hour for both total radioactivity and parent compound. Concentrations of total radioactivity were sustained in blood and plasma through the last sampling time of 144 hours postdose. Concentrations of parent compound were sustained in plasma through the last sampling time of 144 hours postdose in 2 of 3 monkeys, and were similar to plasma total radioactivity concentrations at 8 hours postdose. From 24 to 144 hours postdose, plasma concentrations of total radioactivity were substantially higher than for parent ^{14}C-OLP-1002 plasma concentrations.

The mean C_{max} of parent ^{14}C-OLP-1002 in plasma was 1.96 ng/mL. The mean plasma T_{max} was 0.833 hours. Plasma exposure of parent ^{14}C-OLP-1002 based on AUC extrapolated to infinity ($AUC_{0-\infty}$), was 12.7 ng·h/mL. After reaching C_{max}, plasma concentrations of parent ^{14}C-OLP-1002 declined with a mean $t_{1/2}$ of 84 hours.

1.6. Study Rationale

This is the first time OLP-1002 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data when OLP-1002 is administered SC as single and multiple doses to healthy subjects. This information, together with the pharmacodynamic (PD) and pharmacokinetic (PK) data, will help establish the doses and dosing regimen suitable for future studies in patients. The analgesic effects of OLP-1002 on a capsaicin-induced pain model will also be investigated.

1.7. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. For subjects in the PD assessment groups in Part A there will be some additional discomfort from the capsaicin test. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with OLP-1002 may be found in the Investigator's Brochure[4].

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is to assess the safety and tolerability of single and multiple SC doses of OLP-1002 in healthy subjects.

The exploratory objectives of the study are to evaluate the PD effect of OLP-1002 following single SC doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of single SC doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- incidence and severity of AEs
- vital signs measurements (blood pressure, pulse rate, respiratory rate)
- 12-lead electrocardiogram (ECG) parameters
- incidence of clinical laboratory abnormalities, based on clinical chemistry, hematology, and urinalysis test results
- physical examinations
- injection site assessment.

- demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.

2.2.2. Exploratory Endpoints

The following exploratory objectives will be assessed:

- pain intensity and duration will be assessed by AUC, maximum pain intensity (E_{max}), and time of maximum pain intensity (tE_{max}), calculated using a capsaicin-evoked pain model. The exploratory endpoint of secondary hyperalgesia will be assessed by the area of secondary area of hyperalgesia (Part A only).
- continuous (24-hour) ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval (Part A).
- heat pain threshold measurements and heat pain tolerance measurements.
- For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:

  Primary PK

  - area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])
  - AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)
  - maximum observed plasma concentration (C_{max}) (actual and DN)

  Secondary PK

  - time of the maximum observed plasma concentration (t_{max})
  - apparent plasma terminal elimination half-life ($t_{1/2}$)
- For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:

  Primary PK:

  - AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)
  - $AUC_{0-\infty}$ (actual and DN)
  - C_{max} (actual and DN)

  Secondary PK

  - minimum observed plasma concentration (C_{min})
  - t_{max}
  - $t_{1/2}$
  - observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)
  - observed accumulation ratio based on C_{max} (RAC_{max}).
  - Temporal change parameter (TCP)

Other PK parameters may also be added if deemed necessary.

3. INVESTIGATIONAL PLAN

This will be a double-blind, randomized, placebo-controlled, single and multiple SC dose study conducted in 2 parts.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, PK, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

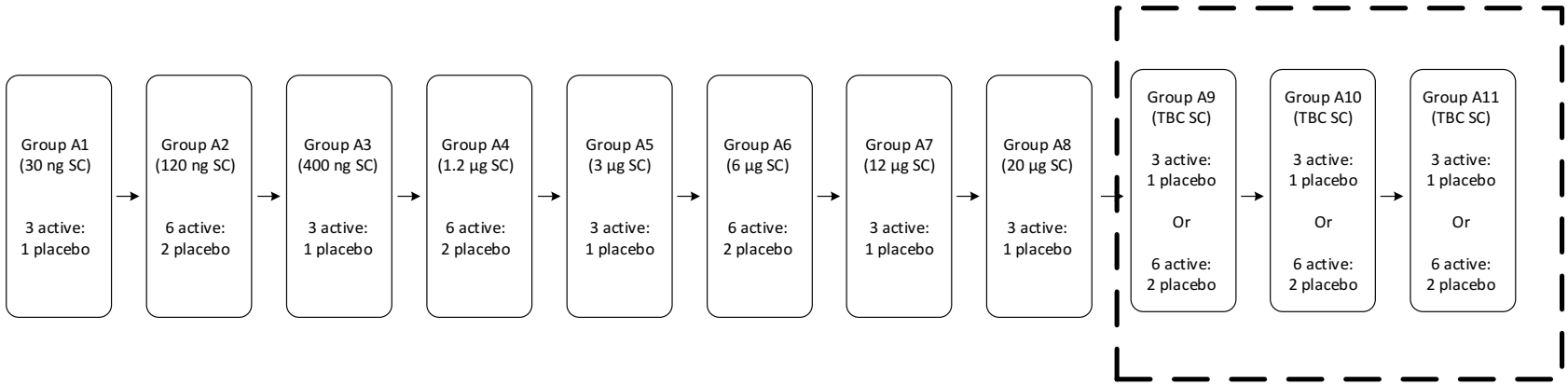
Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 10 (216 hours postdose) from the lower dose levels. For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.

In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, and A6 will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.

Sentinel dosing will be employed for all groups in Part A. To maintain the blind in a 4-subject group, the first subject will be dosed 48 hours before the second subject, and the second subject will be dosed 48 hours prior to the third and fourth subjects. In PD assessment groups, 2 subjects (1 active: 1 placebo) will be dosed 48 hours before the remaining 6 subjects (5 active: 1 placebo).

An overview of the study design is shown in
Figure 1.

Figure 1: Study Schematic (Part A)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
Groups A9 to A11 may be included if required; dose levels will not exceed the maximum proposed dose of 20 µg.
Three groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

3.1.2. Part B

Part B will comprise a multiple-dose, sequential-group study. Overall, 24 subjects will be studied in 3 groups (Groups B1 to B3), with each group consisting of 8 subjects. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety and tolerability (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15.

All subjects will return for non-residential visits on Days 18 (± 2 days), 22 (± 2 days), 25 (± 2 days), and 29 (± 2 days), and for a poststudy visit on Day 57 (± 2 days).

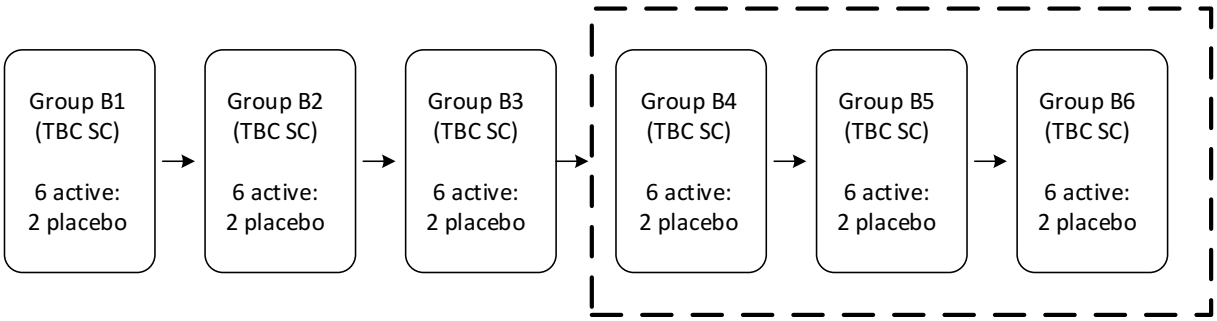
In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from the lower dose levels. Part B may start after a review of the safety, tolerability, and available PK for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

An overview of the study design is shown in Figure 2.

Figure 2: Study Schematic (Part B)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
All doses will be confirmed based on results of Part A; dose levels will not exceed the maximum proposed dose of 20 µg..
Groups B4 to B6 will be included if required.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 12 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Start of Study and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, PK, and PD data (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7]), additional dose groups may be added to the study. The maximum dose for any additional group will not exceed 20 µg. Up to 3 further groups of 8 subjects (6 active: 2 placebo) may be included in Part A, and up to 3 additional groups of 8 subjects (6 active: 2 placebo) may be included in Part B. The requirement for additional groups will be agreed with the Sponsor and documented in the Trial Master File (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential-group, ascending-dose design has been chosen for safety reasons as OLP-1002 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Subcutaneous doses have been chosen for both parts of the study, as this is the intended clinical route of administration.

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety,

tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore, if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.

This study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Continuous ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing in Part A for groups consisting of 4 subjects will be such that there will be 48 hours between the first and second subjects, and 48 hours between the second and remaining 2 subjects in each group. For groups in Part A consisting of 8 subjects, 2 subjects (1 active: 1 placebo) will be dosed 48 hours prior to the remaining 6 subjects.

In Part B, sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.

In Parts A and B, there will be a minimum interval of a 10-minute gap between dosing subjects (when dosed on the same day). Continuation to dose the remaining subjects in a group will be at the Investigator's discretion.

3.4.2. Pharmacodynamic Assessment

Pharmacodynamic assessments will be conducted for subjects in Groups A2, A4, and A6.

Human experimental pain models using healthy volunteers can be used to assess the effect of a drug or treatment under controlled clinical conditions. Capsaicin is a vanilloid responsible for the pungent taste of hot peppers. In mammalian species, capsaicin-induced pain is mediated through Group C nerve fibers following activation of vanilloid 1 transient receptor potential (TRPV1) channels[5]. $Na_v1.7$ has been implicated in controlling neuropeptide release from C-fibers, and suppression of capsaicin-induced neurogenic flair has been demonstrated by an $NA_v1.7$ inhibitor[6].

Several studies have used intradermal capsaicin for human experimental pain studies[7,8]. It has been possible to demonstrate dose-dependent responses, with intradermal injections of 100 µg generally agreed to be the ideal dosage for these studies. Intradermal injection of capsaicin causes a brief stinging/burning pain at the injection site (spontaneous pain) followed by development of secondary hyperalgesia, which can be assessed using equipment such as Von Frey hairs. A study by Gazerani et al.[5] found that the response was site-specific and while peak pain intensity and duration were greatest in the forehead it was found that areas of visible flare and secondary hyperalgesia were significantly larger in the forearm, making the forearm the most suitable site for experimentation.

Covance CRU, Leeds, UK in 2009 performed a validation study using intradermal capsaicin (Covance CRU Study: 9999-004) with between-subject and within-subject variability demonstrating that the assessments can be reliably conducted to assess pharmacological response.

For these reasons, it has been decided to:

- Measure both capsaicin-evoked pain and secondary hyperalgesia.
- Limit the number of capsaicin tests to 3 for each subject (pre-screening, baseline, and 48 hours postdose)
- Exclude subjects who have pain <3 or >9 (using a Visual Analogic Scale [VAS]) at the pre-screening visit from PD assessment groups.

3.5. Selection of Doses in the Study

3.5.1. Starting Dose

The rat has been identified as the most sensitive species in a 13-week SC toxicity study with a 4-week recovery phase (Covance study no. 8355564). The NOAEL was the 100 nmol/kg/dose (462.29 µg/kg/dose). This dose level resulted in C_{max} of 27.6 ng/mL and 24.9 ng/mL in males and females, respectively, and AUC_{0-24} of 174 ng.h/mL and 128 ng.h/mL in males and females, respectively[4]. As the exposure was lower in the female rats these data have been used to calculate the safety margins.

The dose of 462.29 µg/kg/dose corresponds to human equivalent doses (HEDs) of 74.8 µg/kg/dose, which gives a maximum recommended starting dose (MRSD) of 444 µg for a 60-kg human and thus a 15000-fold safety margin to the proposed starting dose of 30 ng and 22-fold margin to the proposed maximum dose of 20 µg. Additionally the NOAEL dose in the cynomolgus monkey was identified as 100 nmol/kg/dose (462.29 µg/kg/dose), which gives a higher HED of 150 µg/kg/dose.

In vivo, doses of 10 pmol/kg/dose (0.0462µg/kg/dose) or less were found to inhibit peripheral acute inflammatory pain. The equivalent human dose for a 60-kg human is 44 ng, thus a dose at which minimal biological effect is anticipated has been selected as the starting dose of 30 ng.

3.5.2. Exposure

Human exposures have been estimated from the pharmacokinetics in the cynomolgus monkey since a non-human primate represents the most closely related species. Approximately dose-proportional exposure was seen in the 13-week toxicity study (Covance study no. 8355565) and ^{14}C pharmacokinetic study (Covance study no. 8355568) over a dose range of approximately 1.1 to 100 nmol/kg (5.06 to 462.29 µg/kg)[4]. However, the lowest dose (5.06 µg/kg) from the ^{14}C study has been used to estimate the human exposures as it is closest to the proposed human dose range and has the sufficient quantifiable data.

The assumptions made in the human exposure estimation were that human exposure would be similar to the cynomolgus monkey and that exposure would be linear with dose. Following a dose of 5.06 µg/kg in the cynomolgus monkey, the C_{max} was 1.96 ng/mL and $AUC_{0-\infty}$ was 12.7 ng.h/mL. The extrapolated exposures at the planned human doses are shown in Table 1 with margins calculated to the exposures at the NOAEL in the female rat.

Table 1: Estimated Human Exposure and Safety Margins to the NOAEL in the Female Rat for Single Dose Administration of OLP-1002

Human dose		Single dose to human		Safety margins for single dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\infty}$
0.03	0.000500	0.000194	0.00125	129000	102000
0.12	0.00200	0.000775	0.00502	32100	25500
0.4	0.00667	0.00258	0.0167	9640	7650
1.2	0.0200	0.0077	0.0502	3210	2550
3	0.0500	0.0194	0.125	1290	1020
6	0.100	0.0387	0.251	643	510
12	0.200	0.0775	0.502	321	255
20	0.333	0.129	0.837	193	153

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

The dosing interval currently anticipated for the multiple-ascending-dose part of this study is 72 hours or 96 hours. Thus the average dosing interval (82 hours) is similar to the half-life determined in the monkey ^{14}C study of 84 hours. Dosing at approximately once per half-life would be anticipated to result in accumulation of around 2-fold. However, higher levels of accumulation were observed (2.28-fold for C_{max} and 3.76-fold for AUC_{0-24}) on Day 88 at the top dose group (100 nmol/kg, 462.28 µg/kg) in the 13-week cynomologus monkey toxicity study following twice-weekly dosing (every 72 or 96 hours). Calculations were performed to estimate the likely human half-life using a standard 1-point allometric approach from the ^{14}C cynomolgus monkey pharmacokinetic study data. The exponents used were 0.75 for apparent total plasma clearance (CL/F) and 1 for apparent volume of distribution (V_z/F) values combined with the average body weight of the animal (3.1 kg) and scaling to a 60 kg human [9–11]. This resulted in a human half-life estimate of 180 h which in turn gave an accumulation estimate of 3.7-fold based upon a dosing interval of 82 h. This further supports the use of the greater than 2-fold accumulation from the 13-week cynomolgus study to estimate exposure following multiple dosing. Multiplication of the exposure estimates for the single ascending

dose by 2.28 for C_{max} and 3.76 for AUC resulted in exposure estimates for multiple dosing presented in Table 2.

Table 2: Estimated Human Exposure and Safety Margin to the NOAEL in the Female Rat for Multiple Dose Administration of OLP-1002

Human dose		Multiple dose to human		Safety margins for multiple dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\tau,ss}$
0.03	0.000500	0.000442	0.00472	56000	27000
0.12	0.00200	0.00177	0.0189	14100	6800
0.4	0.00667	0.00589	0.0629	4230	2030
1.2	0.0200	0.017663	0.189	1410	680
3	0.0500	0.0442	0.472	560	270
6	0.100	0.0883	0.944	282	136
12	0.200	0.177	1.89	141	68
20	0.333	0.294	3.15	85	41
30	0.500	0.442	4.72	56	27

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

3.5.3. Proposed Doses

The proposed IMP dose levels for Parts A and B are shown in Table 3.

Table 3: Proposed Investigational Medicinal Product Dose Levels for Parts A and B

Study Part	Group	Dose (OLP-1002)
Part A	A1	30 ng or placebo
	A2	120 ng or placebo
	A3	400 ng or placebo
	A4	1.2 µg or placebo
	A5	3 µg or placebo
	A6	6 µg or placebo
	A7	12 µg or placebo
	A8	20 µg or placebo
	A9*	TBC or placebo
	A10*	TBC or placebo
	A11*	TBC or placebo
Part B	B1	TBC or placebo
	B2	TBC or placebo
	B3	TBC or placebo
	B4*	TBC or placebo
	B5*	TBC or placebo
	B6*	TBC or placebo

Abbreviations: TBC = to be confirmed
* groups to be included if required.

In Parts A and B, there should not be an increase of > 3-fold between dose levels above 120 ng.

For Part B, dose levels, dosing frequency, and dosing duration will be decided, in consultation with the Sponsor, on the basis of data from Part A of the study. Since predictions of human exposure of OLP-1002 suggest that OLP-1002 concentrations may be not be quantifiable and human data have been estimated from a single species, it is proposed that the highest dose in the multiple-ascending-dose part will be up to 50% of the highest dose in the single-ascending-dose part (ie, if the highest dose in the single-ascending-dose part is 20 µg, the highest dose in the multiple-ascending-dose part will be 10 µg). Therefore, if the predicted accumulation of 3.7-fold occurs, the highest exposure in the multiple-ascending-dose part will not exceed ~2-fold the maximum exposure in the single-ascending-dose part.

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

3.6. Dose Escalation

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 10 (216 hours postdose) from groups that received lower doses of OLP-1002. For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of 3 or 4 subjects, respectively, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

The justification for this is as follows:

- The study drug is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.

- A minimum of 3 subjects receiving the active drug is considered sufficient to characterize the safety profile for OLP-1002.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarizing results from all available safety assessments, will be sent to the Sponsor and a dose-escalation meeting will occur prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PD data may also be reviewed on an ongoing basis. In the event of a disagreement between Sponsor and Investigator on the dose-escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- One or more subjects experience an SAE that is considered to be related to OLP-1002.
- Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase (defined as 3 times the upper limit of normal), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).

If the sponsor deems it appropriate to resume dosing after the internal safety review, it can be done after the approval of a substantial protocol amendment.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Healthy male or females of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) between 18.0 and 28.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, single 12-lead ECG (resting heart rate > 45 bpm and < 90 bpm), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening as assessed by the Investigator (or designee).
4. Willing to abide by the contraception requirements as detailed in Appendix 4.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Any of the following:
    - QTcF > 450 ms confirmed by repeat measurement.
    - QRS duration > 110 ms confirmed by repeat measurement.
    - PR interval > 220 ms confirmed by repeat measurement.
    - findings which would make QTc measurements difficult or QTc data uninterpretable.
    - history of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
4. Female subjects who are pregnant or breastfeeding.
5. History of alcoholism or drug/chemical abuse within 1 year prior to Screening.

6. Alcohol consumption of > 21 units per week for males and >14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
7. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
8. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2).
9. Active skin conditions such as dermatitis, allergy, eczema, psoriasis, or abnormal healing.
10. Tattoos, scars, or moles that in the opinion of the Investigator are likely to interfere with dosing or study assessments at any of the potential injection sites.
11. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days or 5 half-lives of the investigational product, whichever is longer, prior to Check-in.
12. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
13. Use or intend to use any prescription medications/products other than hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptive concomitant medications within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
15. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and/or Sponsor have given their prior consent.
16. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in.
17. Receipt of blood products within 60 days prior to Check-in.
18. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
19. Poor peripheral venous access.
20. Have previously completed or withdrawn from this study or any other study investigating OLP-1002, and have previously received the investigational product.
21. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
22. Part A – PD assessment groups only
    - Subjects considered non-acceptable responders to the intradermal capsaicin test at screening, defined as maximum VAS score of < 3.0 or > 9.0.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number at the time of their randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A, Subjects 101, 102, etc., in Part B Subjects 201, 202, etc.). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal, including:
    - a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),
    - severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),
    - elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),
    - QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),
    - Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),
    - Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Vials of OLP-1002 Injection Solution 100 µg/mL (1.5 mL in 5-mL vials) and the Diluent for OLP-1002 Injection Solution (5 mL in 10-mL vials) will be supplied by the Sponsor, along with the batch/lot number and Certificate of Analysis. The Diluent for OLP-1002 Injection Solution will also be used as the Placebo formulation. A certificate of batch certification and release, authorized by a Qualified Person in the European Union (EU) will also be issued, by a Covance CRU Qualified Person, for each batch of IMP imported into the EU.

The IMPs will be stored according to the instructions on the label at the CRU in a location that is locked with restricted access.

Dose solutions (OLP-1002 Injection Solution diluted with the Diluent for OLP-1002 Injection Solution) will be prepared by Covance CRU Pharmacy staff in accordance with instructions provided in the Pharmacy Manual. The Placebo formulation will be the Diluent for OLP-1002 Injection Solution without further manipulation.

5.2. Study Treatment Administration

Subjects will be administered the IMP in numerical order. OLP-1002 will be administered by SC injection in the upper arm. If subcutaneous dosing of OLP-1002 in the upper arm is not possible, the subject may be dosed in the abdomen at the Investigator's discretion. For subjects in Groups A2, A4, and A6, dosing will be on the opposite arm to the intradermal capsaicin test.

5.3. Randomization

The randomization code will be produced by the statistics department at Covance using a computer-generated pseudo-random permutation procedure. In Part A, 1 subject in groups

consisting of 4 subjects, and 2 subjects in groups consisting of 8 subjects, will be randomly assigned to receive placebo. In Part B, 2 subjects per group will be randomly assigned to receive placebo. All other subjects in a group will be randomized to receive OLP-1002.

Prior to the start of the study, a copy of the master randomization code will be supplied into the Covance CRU pharmacy staff (in sealed envelopes).

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo solution will be identical in appearance to the OLP-1002.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

To maintain the blind, the Investigator will be provided with sealed randomization code-break envelopes for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose-escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

All doses of IMP will be administered by suitably qualified study site staff.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription medications/products from 14 days prior to dosing until the Follow-up visit, and non-prescription medications/products from 7 days prior to dosing until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests. On dosing days, subjects will receive a light breakfast approximately 2 hours prior to dosing. Meals will be provided as appropriate at other times and water will be freely available at all times.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until the Follow-up visit.

Xanthine-containing foods and beverages will not be allowed from 36 hours before Check-in until Discharge from the site. Xanthine-containing foods and beverages will also not be allowed form 36 hours before non-residential site visits.

Chili pepper/hot sauce will not be allowed for 48 hours prior to Check-in for all subjects. Subjects in Groups A2, A4, and A6 will not be allowed chili pepper/hot sauce for 48 hours prior to their pre-screening visit.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until Discharge. Following discharge, up to 2 units/day of alcohol are permitted until 36 hours before each non-residential visit and the Follow-up visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 3 days before Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during this

time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit. Subjects should not be in receipt of blood products for 60 days prior to check-in.

6.6. Other Restrictions

Subjects in Groups A2, A4, and A6 will not be allowed to shower within 1 hour prior to the capsaicin-evoked pain tests at prescreening, predose, and postdose.

Subjects will not be allowed to apply moisturizing creams or oils to the dosing site within 1 hour prior to dosing, or to the assessment site within 1 hour prior to the capsaicin-evoked pain test.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- vital signs
- blood samples
- cardiac monitoring/ECG extractions
- any other procedures.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, PK analysis will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the

event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Pharmacodynamic Assessments

Capsaicin intradermal test will be performed for subjects in Groups A2, A4, and A6. Each subject will be tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).

7.2.1. Capsaicin-evoked Pain Model

The capsaicin model will be conducted by intradermal injection of capsaicin (100 µg in 100 µL of sterile saline containing 8% [w/w] Tween 80) into the skin of the anterior aspect of the forearm, midway between the elbow and the wrist. The bleb area (wheal) will be a sign of local plasma extravasation. An assessment of the pain intensity related to capsaicin injection will be estimated by repeated use of a VAS from injection to 5 minutes post-injection or until the pain intensity returned to zero. The AUC, E_{max}, and tE_{max} will be calculated and reported using dedicated software.

7.2.2. Secondary Hyperalgesia

The area of secondary hyperalgesia will be quantified with a 60-g weighted von Frey hair, by stimulating along 8 linear paths (4 vectors crossing at the location of the injection site) arranged vertically and horizontally around the stimulation site in 5-mm steps (starting approximately 6 cm away from the injection site). The area of secondary hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection.

7.3. Safety and Tolerability Assessments

Safety and tolerability assessments will be conducted at the times indicated in the Schedule of Assessments (Appendix 6). Timepoints may be adjusted based on an ongoing review of the data, and additional assessments may be conducted if deemed necessary by the Investigator or designee.

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked

about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a follicle-stimulating hormone (FSH) test and pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

Subjects must be supine for at least 5 minutes before blood pressure, pulse rate, and respiratory rate measurements.

7.3.4. Electrocardiogram

7.3.4.1. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value > 500 msec
- QTcF change from the mean baseline (Day 1 predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.4.2. Continuous (24-hour) Electrocardiogram

At the times indicated in the Schedule of Assessments (Appendix 6), continuous (24-hour) ECGs will be performed.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint. Each extraction will last for 5 minutes. Environmental distractions (eg, television, playing games, radio, conversation) should be avoided during the pre-ECG time window.

Continuous 24-hour ECGs are not planned for Part B of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.3.5. Heat Pain Threshold Test

Heat pain threshold tests will be conducted at the times indicated in the Schedule of Assessments (Appendix 6).

A computer-controlled thermal sensory analyzer device will be used to measure the heat pain threshold and tolerance level of the subjects. The heat pain assessments will be conducted on the subject's thigh.

Heat Pain Threshold:

For heat pain threshold measurements, the thermode will be placed directly on the skin of the right thigh, within an area selected before the start of the experiment and defined by surgical marking. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in

their dominant hand, to indicate when the heat pain threshold (first sensation of heat pain) is reached by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Heat Pain Tolerance:

For heat pain tolerance measurements, the thermode will be placed within the same surgically marked skin area of the anterior side of the right thigh, which was used to assess heat pain threshold. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in their dominant hand, to indicate when the heat-evoked pain has reached an intensity that is no longer tolerable, by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Safety Precautions

As there is a risk that OLP-1002 may affect the heat pain threshold, Covance CRU will put appropriate safety measures in place to ensure that subjects are not exposed to extremes of temperature when taking a shower or consuming hot drinks. During the heat pain safety assessments, the cut-off temperature for either test is 53 °C in order to prevent skin injury.

7.3.6. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

7.3.7. Body Weight and Height

Body weight (in underclothes) and height will be recorded at the times indicated in the Schedule of Assessments in Appendix 6. BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{body weight (kg)}}{(\text{height [m]})^2} \quad (\text{kg/m}^2)$$

7.3.8. Injection Site Assessments

Injection site assessments will be made at the times indicated in the Study Plan (Appendix 6).

Assessments will involve evaluation of the dosing site for the following criteria:

- Pain will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Requires medical intervention greater than analgesia

- Redness will be assessed by estimating the size of the red patch at the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm	51-100 mm	More than 100 mm	Requires medical intervention greater than analgesia

- Swelling will be assessed by estimating the size of the raised area around the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm and does not interfere with activity	51-100 mm or interferes with activity	More than 100 mm and prevents daily activity	Requires medical intervention greater than analgesia

In addition, how the swelling affects the subject in their daily routing activities will be considered.

- Tenderness will be evaluated using the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Mild pain to touch	Moderate Pain to touch	Severe pain to touch	Requires medical intervention greater than analgesia

- Bruising and ulceration will be evaluated as being present or absent.

Local tolerability ratings of ≥Grade 3 and the presence of ulceration will be recorded as an adverse event.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. In order to achieve PD endpoints in Part A, additional subjects will be included in 3 groups (8 subjects in total; 6 active: 2 placebo). Up to 3 additional groups may be added to Part A, consisting of either 4 subjects (3 active; 1 placebo) or 8 subjects (6 active; 2 placebo). Up to 3 additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.2. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of

OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

8.4. Pharmacodynamic Analyses

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned.

8.5. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- Mild: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but posing no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- Not Related: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- Unlikely Related: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- Related: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at the Follow-up visit will be followed up, where possible,

until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit (CRU). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Covance Drug Safety Services (DSS) Europe, Maidenhead, UK are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to DSS and the Sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Covance DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 2 working days of the initial notification to DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy reported by female subjects or

the female partners of male subjects should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total protein Urea	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[a]:	**Drug screen[b]:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test MDMA Alcohol breath test	Follicle-stimulating hormone[a] Serum pregnancy test (human chorionic gonadotropin)[a] Urine pregnancy test[c]

[a] Only analyzed at Screening.
[b] Only analyzed at Screening and Check-in.
[c] A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	19	76
Clinical laboratory evaluations (excluding serology)	7.5	6	45
Serology	3.5	1	3.5
Total:			124.5

Part B

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	29	116
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			194.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject during the study will not exceed that donated during a standard blood donation (approximately 500 mL).

Appendix 4: Contraception Guidance

Definitions

Females of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Females of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary highly effective and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary highly effective methods of contraception include:

- surgical method performed at least 3 months prior to the Screening visit:
  - bilateral tubal ligation
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)
- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects can only choose a cervical cap or diaphragm if they have already had a prescription and fitting by their healthcare provider to ensure protocol requirements are met. Female subjects of childbearing potential should refrain from donation of ova from Check-in until 90 days after the Follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide
- vasectomised male subject (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success).

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the Follow-up visit.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the Follow-up visit.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a

public registry, all identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled and randomized subject, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

Study Plan – Part A (Single Dose)

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Urine drugs of abuse screen		X	X							
Alcohol breath test		X	X							
Cotinine test		X	X							
Serology		X								
Hormone panel		X								
Urine pregnancy test[a]		X	X							X
Informed consent	X	X								
Study residency:										
Check-in			X							
Check-out					Day 3 (48 hours postdose)					
Non-residential visit	X	X				X	X	X	X	X
Study drug administration:					Day 1 (0 hours)					
Safety and tolerability:										
Adverse event recording		X	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording		X	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature		X			Predose, 1, 2, 4, 8, 24 (± 1 hour), and 48 hours postdose	X	X	X	X	X

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Supine 12-lead ECG		X			Predose, 4, 24 (± 1 hour) and 48 hours postdose		X		X	X
Continuous ECG extraction[b,c]				-24, -23.5, -23, -22.5, -22, -21.5, -21, -20, -18, -16, -12 hours	Day 1: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours					
Heat pain threshold test (heat pain threshold and heat pain tolerance)					Day 1: predose, 2, 4, 12, and 24 hours postdose (± 1 hour)					
Clinical chemistry, haematology, and urinalysis		X	X		48 hours postdose		X		X	X
Height and BMI		X								
Body weight		X	X							X
Physical examination		X								
Symptom-directed physical examination					Prior to discharge		X		X	X

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Injection site assessment					Predose, 1, 2, 4, 8, 24, 48 hours postdose		X		X	X
Pharmacokinetics[e]										
Blood sampling					Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose	X	X	X	X	X
Pharmacodynamics[d]:										
Intradermal capsaicin test (capsaicin-evoked pain and secondary hyperalgesia measurement)	X		X		Day 2 (The area of secondary area of hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection)					

Abbreviations: BMI = body mass index; ECG = electrocardiogram.
[a] A positive urine pregnancy test result will be confirmed with a serum pregnancy test.
[b] All times are relative to dosing with OLP-1002.
[c] Continuous ECG recording may begin at approximately 25 hours before dosing to allow for checks to be completed prior to the first extraction timepoint and will continue for 24 hours postdose, ie, until after the last timepoint for ECG extraction (24 hours postdose). At timepoints for ECG extractions, subjects will be supinely resting for a total of 15 minutes (10-minute supine rest period, 5-minute extraction). Data will be archived for potential future analysis and will not be available for review during the study.
[d] Pharmacodynamic assessment groups only.
[e] PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

Study Plan – Part B (Multiple Dose)

	Screening	Day -1	Days 1-15	Day 18 (± 2 days)	Day 22 (± 2 days)	Day 25 (± 2 days)	Day 29 (± 2 days)	Poststudy (Day 57 ± 2 days)
Inclusion/exclusion criteria	X							
Demographic data	X							
Medical history	X							
Urine drugs of abuse screen	X	X						
Alcohol breath test	X	X						
Cotinine test	X	X						
Serology	X							
Hormone panel	X							
Urine pregnancy test[a]	X	X			X		X	X
Informed consent	X							
Study residency:								
Check-in		X						
Check-out			Day 15 (48 hours postdose)					
Non-residential visit	X			X	X	X	X	X
Study drug administration:			Days 1, 4, 7, 10, and 13					
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature	X		Day 1: predose, 1, 2, 4 and 8 hours postdose Day 2, Day 4 (postdose), Day 5, Day 7 (postdose), Day 9, Day 10 (postdose), Day 12, Day 13: predose, 1, 2, 4 and 8 hours postdose, and Day 15	X	X	X	X	X

	Screening	Day -1	Days 1-15	Day 18	Day 22	Day 25	Day 29	Poststudy (Day 57 ± 2 days)
Heat pain threshold test (heat pain threshold and heat pain tolerance)	X		Day 1 and Day 13: predose, 1, 2, 4, 8, 24 hours postdose					
Supine 12-lead ECG	X		Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Clinical chemistry, haematology, and urinalysis	X	X	Days 2, 5, 9, 12, 17		X		X	X
Height and BMI	X							
Body weight	X	X						X
Physical examination	X							
Symptom-directed physical examination			Days 1, 4, 7, 10, 13		X		X	X
Injection site assessment			Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Pharmacokinetics:								
Blood sampling[b]			Day 1 and Day 13: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose Days 4, 7, 10 Predose Day 15	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram.
[a] Positive urine pregnancy test results will be confirmed with a serum pregnancy test.
[b] PK timepoints will be reviewed based on emerging data and may be updated.

Appendix 7: Protocol Amendment Summary of Changes

Protocol Amendment 3 (Version 2.2; 12 December 2018)

This non-substantial amendment has been issued to include a clinical laboratory assessment on Day -2 in Part A.

Appendix 3

Additional clinical laboratory sample added to Part A. Total blood volume withdrawn in Part A updated to 124.5 mL.

Appendix 6 Study Plan (Part A)

Clinical chemistry, haematology, and urinalysis assessment added on Day -2.

Protocol Amendment 2 (Version 2.1; 29 November 2018)

This non-substantial amendment has been issued to correct minor inconsistencies in PK sampling timepoints, data cut off for dose escalation, clinical laboratory assessment timepoints, and the synopsis. Additionally, details of the injection site assessments have been added to the protocol.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Synopsis: Endpoints

Text added:

Safety:
Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, **heat pain threshold and tolerance,** and physical examinations.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from groups that received lower doses of OLP-1002.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to

Day **10** (**216** hours postdose) from groups that received lower doses of OLP-1002.

Section 7.3.8

Entire section added to describe injection site assessments.

Appendix 3

Total blood volume for PK analysis (76 mL) added.

Appendix 6 - Schedule of assessments Part A

24 hour postdose continuous ECG recording timepoint added.

Appendix 6 - Schedule of assessments Part B

Clinical chemistry, haematology, and urinalysis for Days 1-15 previously read:

Days 2, ~~4~~, ~~7~~, ~~10~~,~~13~~

Clinical chemistry, haematology, and urinalysis for Days 1-15 now reads:

Days 2**, 5, 9, 12, 17**

PK blood sampling for Days 1-15 previously read:

Day 1 and Day ~~15~~: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, ~~8,~~ ~~11, 15~~ Predose

PK blood sampling for Days 1-15 now reads:

Day 1 and Day **13**: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, **7, 10** Predose
Day 15

Protocol Amendment 1 (Version 2; 02 October 2018)

This amendment has been generated following the non-acceptance of the original protocol (version 1) by the Medicines and Healthcare products Regulatory Agency (MHRA) on 20 September 2018. All changes made have been in response to comments provided by the MHRA.

The primary changes in this amendment are:

1. Inclusion of PK sampling in Parts A and B:
    - PK objective and exploratory endpoints added (Section 2).

- Discussion of PK included Section 3.4.
- PK stopping criteria added to Section 3.7.
- PK assessments included in Section 7.1.
- PK population and analysis (Section 8.2.1).
- Blood volumes updated to include samples for PK assessments (Appendix 3).

2. Exclusion and stopping criteria updated
    - Women who are pregnant or breastfeeding have been excluded from the study (Section 4.2).
    - Liver function tests, tachycardia, and hypertension stopping criteria have been updated (Section 3.7 and Section 4.4).
    - Stopping criteria for SAEs and serious AEs have been added (Section 3.7 and Section 4.4).
3. Safety, tolerability, and PK data up to Day 22 in Part B will be reviewed prior to dose escalation (Section 3.1.2).
4. Sentinel dosing included in Part B (Section 3.1.2).
5. It has been specified that the maximum dose for additional groups will not exceed 20 µg (Section 3.5.3).

Minor changes:

1. Additional clinical laboratory evaluations have been included on Day 14 in Part A.
2. The definition of the Safety population has been updated to include all subjects who receive OLP-1002.
3. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Section 1.6

Previously read:

This information, together with the pharmacodynamic (PD data, will help establish the doses and dosing regimen suitable for future studies in patients.

Now reads:

This information, together with the pharmacodynamic (PD) **and pharmacokinetic (PK)** data, will help establish the doses and dosing regimen suitable for future studies in patients.

Section 2.1

Objective added:

Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

Section 2.2.1

Endpoint added:

- **demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.**

Section 2.2.2

Endpoints added:

- **For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])**
  - **AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)**
  - **maximum observed plasma concentration (C_{max}) (actual and DN)**

  Secondary PK

  - **time of the maximum observed plasma concentration (t_{max})**
  - **apparent plasma terminal elimination half-life ($t_{1/2}$)**
- **For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)**
  - **$AUC_{0-\infty}$ (actual and DN)**
  - **C_{max} (actual and DN)**

  Secondary PK

  - **minimum observed plasma concentration (C_{min})**
  - **t_{max}**
  - **$t_{1/2}$**
  - **observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)**

- **observed accumulation ratio based on C_{max} (RAC_{max}).**
- **Temporal change parameter (TCP)**

Other PK parameters may also be added if deemed necessary.

Section 3.1.1

Previously read:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from the lower dose levels.

Now reads:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, **PK,** and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day **10** (**216** hours postdose) from the lower dose levels. **For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.**

Figure 1 – footnote

Text added:

Groups A9 to A11 may be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Figure 2 – footnote

Text added:

Groups B4 to B6 will be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Section 3.1.2

Previously read:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. ~~There will be no sentinel dosing in Part B.~~ For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from the lower dose levels. Part B may start after a review of the safety ~~and~~ tolerability for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Now reads:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed

following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from the lower dose levels. Part B may start after a review of the safety**,** tolerability**, and available PK data** for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Section 3.3

Previously read:

Following review of the safety, tolerability, and PD data, additional dose groups may be added to the study.

Now reads:

Following review of the safety, tolerability, **PK,** and PD data **(where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7])**, additional dose groups may be added to the study. **The maximum dose for any additional group will not exceed 20 µg.**

Section 3.4

Previously read:

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data

may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

~~Pharmacokinetic analysis will not be conducted in this study. T~~he bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose~~s~~ would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. ~~Thus, the additional burden of sampling procedures would not be justified by the quality of the data which it would generate.~~

Now reads:

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing

regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. **Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable.** It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. **In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.**

Section 3.4.1

Previously read:

In Part B, ~~all subjects in a group will be dosed on the same day~~. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3).

Now reads:

In Part B, **sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the**

remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). **If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.**

Section 3.5.3

Text added:

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of ~~5~~ subjects, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002. **For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous**

groups will be reviewed prior to dose escalation.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. **Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.**

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of **3 or 4** subjects**, respectively**, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Section 3.7

Previously read:

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in ~~liver function tests (~~aspartate aminotransferase, alanine aminotransferase~~,~~ alkaline phosphatase ~~and total bilirubin)~~ defined as 3 times the upper limit of normal in ~~3~~ or more subjects in a group ~~(~~confirmed with repeat testing~~)~~.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.

Now reads:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- **One or more subjects experience an SAE that is considered to be related to OLP-1002.**
- **Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.**
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase **or** alkaline phosphatase **(**defined as 3 times the upper limit of normal**), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be** confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- **The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).**

Section 4.2

Exclusion criteria added:

4. Female subjects who are pregnant or breastfeeding.

Section 4.4

Previously read:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal

Now reads:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal**, including:**
  - **a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),**
  - **severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),**
  - **elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),**
  - **QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),**
  - **Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),**
  - **Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).**

Section 7.1

Section added:

7.1 Pharmacokinetic Assessments

7.1.1 Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, only samples collected from subjects that received >12 µg OLP-1002 will be initially analyzed. If PK data is quantifiable at concentrations of OLP-1002 >12 µg, samples from lower dose groups will be retrospectively analyzed. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will

be detailed in a separate document.

7.1.2 Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

Section 8.2

Previously read:

8.2.~~1~~ Pharmacodynamic population

The PD population will include all subjects who received at least 1 dose of ~~study treatment~~ OLP-1002 or placebo and for whom PD can be evaluated.

8.2.~~2~~ Safety Population
The safety population will include all subjects who received at least 1 dose of ~~study treatment~~ or placebo ~~and have at least 1 postdose safety assessment~~.

Now reads:

8.2.1 Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.**2** Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.**3** Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3 Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma and urine concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

Appendix 3

Table updated:

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis*	**4**	**19**	**76**
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			~~33.5~~**109.5**

Part B

	Volume per blood sample (mL)	**Maximum number of blood samples**	**Total amount of blood (mL)**
Pharmacokinetic analysis	**4**	**29**	**116**
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			~~78.5~~**194.5**

Appendix 6

PK and Blood sampling rows added to the schedule of events for Part A and Part B. In the Schedule of events for Part A, footnote e was added. In the Schedule of events for Part B, footnote b was added.

Clinical chemistry, hematology, and urinalysis was added to the Schedule of events for Part A on Day 14.

Protocol

OLP-1002 – A First-in-human, Double-blind, Placebo-controlled, Single and Multiple Subcutaneous Dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Male and Female Subjects

Protocol Status: Final
Protocol Date: 29 November 2018
Protocol Version: 2.1

Investigational Product: OLP-1002

Protocol Reference Number: OLP-1002-001
Covance Study Number: 8379789
EudraCT Number: 2018-003085-13

Sponsor:
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Sponsor Signatory:
[redacted]

Principal Investigator:
[redacted]

SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

December 03, 2018
Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

[redacted]

[redacted]
Principal Investigator

03 DEC 2018
Date

STUDY IDENTIFICATION

Sponsor	OliPass Corporation Ace Dongbaek Tower 20th Floor 16 Beon-gil, 16-4 Dongbaek Jungang-ro Giheung, Yongin, Gyeonggi 17015 Republic of Korea
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Medical Monitor (24-hour emergency medical contact)	[redacted]
Study Site	Covance Clinical Research Unit Ltd. Springfield House, Hyde Street, Leeds, LS2 9LH United Kingdom
Principal Investigator	[redacted] Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH United Kingdom [redacted]
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SYNOPSIS

Title of study: OLP-1002 – A first-in-human, double-blind, placebo-controlled, single and multiple subcutaneous dose, safety, tolerability, pharmacokinetic, and pharmacodynamic study in healthy male and female subjects
Objectives: The primary objective of the study is to assess the safety and tolerability of single and multiple subcutaneous doses of OLP-1002 in healthy subjects. The exploratory objectives of the study are to evaluate the pharmacodynamic effect of OLP-1002 following single subcutaneous doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of a single subcutaneous doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.
Study design: This will be a double-blind, randomized, placebo-controlled, single and multiple subcutaneous dose study conducted in 2 parts, including healthy male and female subjects.
Number of subjects: Part A: 44 subjects will be studied in 8 groups (5 groups of 4 and 3 groups of 8). Part B: 24 subjects will be studied in 3 groups (Groups B1 to B3). Up to 24 additional subjects may be recruited into Part A and Part B of the study if required.
Diagnosis and main criteria for inclusion: Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 28.0 kg/m^2 (inclusive).
Investigational products, dose, and mode of administration: Test product: OLP-1002 Proposed dose levels for Part A: 30 ng, 120 ng, 400 ng, 1.2 µg, 3 µg, 6 µg, 12 µg, and 20 µg. Proposed dose levels for Part B: the doses for Part B will be decided in consultation with the Sponsor and on the basis of data from Part A of the study. The highest dose in Part B will be up to 50% of the highest dose in Part A. Administration route: subcutaneous
Reference product and mode of administration: Reference product: placebo Administration route: subcutaneous
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to Follow-up): approximately 8 weeks for Part A and approximately 12 weeks for Part B.

Endpoints:

Pharmacodynamics:

In Part A, the analgesic effect of OLP-1002 will be investigated in 3 groups consisting of 8 subjects (6 active: 2 placebo) using experimental capsaicin-evoked pain methods. Measurement of capsaicin-evoked pain will be performed at pre-screening, baseline and on Day 2, and secondary hyperalgesia at 5 and 30 minutes post-capsaicin injection. Continuous electrocardiogram (ECG) recording will be conducted to investigate the effect of OLP-1002 on cardiac function.

Safety:

Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, heat pain threshold and tolerance, and physical examinations.

Pharmacokinetics:

In Part A, the following PK parameters will be determined where possible: area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$), maximum observed plasma concentration (C_{max}), time of the maximum observed plasma concentration (t_{max}), and apparent plasma terminal elimination half-life ($t_{1/2}$). PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

In Part B, the following PK parameters will be determined where possible: AUC over a dosing interval ($AUC_{0-\tau}$), $AUC_{0-\infty}$, $C_{max,}$ minimum observed plasma concentration (C_{min}), t_{max}, $t_{1/2}$, observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$), observed accumulation ratio based on C_{max} (RAC_{max}), and Temporal change parameter (TCP). PK samples from all groups in Part B will be analyzed.

Statistical methods:

Pharmacodynamics:

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of pharmacodynamic data is planned.

Safety:

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

Pharmacokinetics:

Individual plasma concentrations and PK parameters of OLP-1002 will be listed and summarized using descriptive statistics. Individual and mean OLP-1002 concentration-time profiles will be presented graphically.

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours postdose
BMI	body mass index
C_{max}	maximum observed plasma concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSA	clinical study agreement
DN	Dose normalized
DRG	dorsal root ganglion
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
E_{max}	maximum pain intensity
FCA	Freund's Complete Adjuvant
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SC	subcutaneous(ly)
SNL	spinal nerve ligation
$t_{1/2}$	elimination half-life
tE_{max}	time of maximum pain intensity
T_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
VAS	Visual Analogic Scale
VGSC	voltage-gated sodium channel

1. INTRODUCTION

1.1. Overview

OLP-1002 is a novel peptide nucleic acid (PNA) derivative which acts as a specific voltage-gated sodium channel (VGSC) protein ($Na_v1.7$) inhibitor, and is being developed by OliPass for the treatment of pain.

The $Na_v1.7$ protein is a subtype of VGSCs. $Na_v1.7$ is particularly important in nociception and pain signaling, with congenital loss-of-function mutations in $Na_v1.7$ resulting in the inability to experience pain. Selective $Na_v1.7$ inhibitors are believed to have the potential to treat severe pain safely[1]. The active sites of VGSC subtypes are virtually indistinguishable by their 3-dimensional structure and thus the discovery of selective $Na_v1.7$ small molecule inhibitors has been extremely challenging. Since inhibition of $Na_v1.5$ subtype elicits long QT cardiotoxicity, inhibition of $Na_v1.5$ subtype should be avoided at therapeutic doses.

To date, there are several $Na_v1.7$ inhibitors claimed to be selective that have been evaluated in human subjects:

- Vixotrigine (formerly known as raxatrigine) inhibits $Na_v1.7$ as well as other VGSC subtypes. Vixotrigine is in phase III clinical development for trigeminal neuralgia. Due to the limited $Na_v1.7$ selectivity over $Na_v1.5$, vixotrigine was evaluated primarily in patients with a low heart risk.
- Funapide is a $Na_v1.7$ inhibitor with limited $Na_v1.7$ selectivity, and was in phase IIb clinical trials as of July 2014. Although funapide showed analgesic activity in a small number of erythromelalgia patients, dose-limiting adverse events (AEs), including dizziness and somnolence, were observed[2]. The central nervous system (CNS) AEs were due to its poor $Na_v1.7$ selectivity.
- PF-05089771 is a $Na_v1.7$ selective inhibitor with a claimed $Na_v1.7$ selectivity of > 2000-fold versus other subtypes of sodium channel and was evaluated in patients of erythromelalgia or dental pain. It is thought low drug concentrations achieved in the target tissue could be a possible explanation for its poor analgesic activity in human patients[3].

OLP-1002 is fully complementary to a 14-mer RNA sequence spanning the junction of intron 4 and exon 5 in the human SCN9A pre-mRNA which codes for the $Na_v1.7$ channel. OLP-1002 yields SCN9A mRNA splice variant(s) encoding variant $Na_v1.7$ protein(s) lacking the sodium channel activity (ie, a non-functional channel), thereby inhibiting $Na_v1.7$ channel function.

1.2. Summary of Nonclinical Pharmacology

1.2.1. In Vitro Pharmacology Studies

Overall, results from the in vitro pharmacology studies showed OLP-1002 elicits responses consistent with its designed function[4]. It inhibits SCN9A mRNA expression and yields the

$Na_v1.7$ variant protein or proteins lacking sodium channel activity. Its effects are highly selective, which may provide for an improved margin of safety compared to other $Na_v1.7$ inhibitors.

OLP-1002 at 1 to 100 zM in PC3 prostate carcinoma cells induced exon skipping and yielded SCN9A mRNA splice variant(s) encoding a $Na_v1.7$ variant protein or proteins lacking sodium channel activity.

In rat dorsal root ganglion (DRG) neuronal cells, OLP-1002 at 1000 zM inhibited $Na_v1.7$ protein expression by > 50%, while OLP-1002R at 100 and 1000 zM inhibited $Na_v1.7$ expression almost completely. As OLP-1002R is fully complementary to rat SCN9A pre-mRNA, OLP-1002R would be predicted to be more potent than OLP-1002 in this cell type.

SCN9A mRNA expression level was evaluated by quantitative polymerase chain reaction (qPCR). OLP-1002 inhibited the expression of the SCN9A mRNA in PC3 cells with sub-attomolar potency.

In SH-SY5Y human neuroblastoma cells stimulated with tumor necrosis factor (TNF)-1α to upregulate the expression of SCN9A mRNA, OLP-1002 decreased expression by 46% to 49% at 1 fM to 10 pM. In rat DRG neuronal cells, OLP-1002 at 1 fM significantly decreased SCN9A mRNA expression by 54%.

In rat DRG neuronal cells, OLP-1002 markedly and significantly inhibited the sodium current by 77% at 0.1 aM and 73% at 1 aM, while for OLP-1002R, the inhibition was 66% at 0.1 aM and 70% at 1 aM. Given that rat DRG neuronal cells express various subtypes of sodium channel, the observed inhibitions of 66% to 77% correspond to the complete knockout of the $Na_v1.7$ sodium channel subtype with OLP-1002 or OLP-1002R.

The $Na_v1.7$ selectivity over $Na_v1.5$ was evaluated in H9C2 rat cardiomyocytes which are known to abundantly express the rat $Na_v1.5$ sodium channel subtype. Following incubation with OLP-1002 or OLP-1002R at 1 aM or 1 pM, there were no notable decreases in the sodium current. Considering that OLP-1002 and OLP-1002R inhibit the expression of $Na_v1.7$ protein at 1 aM or lower in rat DRG neuronal cells, the $Na_v1.7$ selectivity of OLP-1002 and OLP-1002R over $Na_v1.5$ is estimated to be in excess of one million-fold. Such a large $Na_v1.7$ selectivity over $Na_v1.5$ has not been realized with small molecule $Na_v1.7$ inhibitors, suggesting that OLP-1002 potentially offers pain management with much greater cardiovascular safety.

1.2.2. In Vivo Pharmacology Studies

Spinal nerve ligation (SNL) has been widely applied as a rat model for neuropathic pain. OLP-1002 and OLP-1002R were found to be very potent, but highly variable in potency, in reversing neuropathic allodynia in this model. Analyses of the therapeutic potency strongly suggested that a marked proportion of subcutaneously (SC) administered OLP-1002 or OLP-1002R may have been topically delivered directly to the spinal nerves exposed in the dorsal cavity created during the SNL modelling. In addition, the variability of the therapeutic potency may be due to a variable degree of healing of the SNL surgery wound. If an animal

recovers slowly, the animal tends to be left with a dorsal cavity. Therefore, estimations of potency in these studies with this model should be treated with caution.

In one study using the SNL model, allodynia in rats was slowly and gradually reversed by OLP-1002 SC administered at nominal doses of 1, 3, and 6 pmol/kg once every 2 days (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). As the onset time for pain reduction was 4 days, the doses used were not sufficient for fast onset of activity. In this study, the animals should have reasonably recovered from the dorsal wound, and therefore less susceptible to topical delivery directly to the exposed spinal nerves. However, in another study in this model, when OLP-1002 was intraperitoneally (IP) administered once every 3 days to avoid the likelihood of local delivery to the spinal nerves, OLP-1002 surprisingly reversed the allodynia at 5 fmol/kg, and was superior or comparable to pregabalin 30 mg/kg, a gold standard for neuropathic pain studies. The high potency shown at 5 fmol/kg IP strongly suggests the possibility that OLP-1002 is efficiently absorbed by the enteric nervous system, travels to the spinal cord, and then redistributes to the spinal nerves of the SNL ligation. This opens the possibility of efficient oral delivery of OLP-1002 to the spinal cord.

When evaluated for their ability to reverse the inflammatory pain in rats inflicted with Freund's Complete Adjuvant (FCA)-induced severe paw inflammation, OLP-1002 at 300 pmol/kg and OLP-1002R at 100 pmol/kg significantly reversed the thermal hyperalgesia, and both were more effective than pregabalin 30 mg/kg.

Paw burn injury induces hyperalgesia in rats and is known to upregulate $Na_v1.7$ expression in the L5 and L6 DRGs of the affected side. Burn injury induces a far weaker degree of paw inflammation than FCA-induced paw inflammation. OLP-1002 SC administered inhibited the thermal hyperalgesia in paw burn injury in a dose-dependent manner. At 25 fmol/kg, OLP-1002 did not inhibit thermal hyperalgesia. Although OLP-1002 at 625 fmol/kg significantly inhibited the thermal hyperalgesia, the efficacy was moderate and weaker than pregabalin 30 mg/kg. This suggests that SC dosing does not offer the local topical delivery to spinal nerves in this model as seen in rats without a dorsal cavity wound. In this study, the $Na_v1.7$ expression in the DRG of the burn injury side significantly decreased by 58% with 625 fmol/kg OLP-1002, validating the target engagement for analgesic activity.

An intraplantar injection of formalin induces severe acute pain. The contributors to acute pain are known to be complex and require further elucidation. However, acute peripheral inflammation is known to contribute much to Phase II Pain (pain from 10 to 40 min after the formalin injection). In this model, OLP-1002 significantly inhibited Phase II Pain at comparable or saturated efficacy when SC administered at 10 to 100 pmol/kg (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). Thus peripheral acute inflammatory pain could be treated with 10 pmol/kg or less.

1.2.3. Ex Vivo Pharmacology Studies

One day post-SC injection, OLP-1002 and OLP-1002R at 100 pmol/kg significantly inhibited the expression of $Na_v1.7$ protein by 39% and 57%, respectively, in the spinal cord of rats subjected to SNL.

In other rats subjected to SNL, OLP-1002R slowly and gradually reversed the allodynia in a dose-dependent manner. OLP-1002R at 30 fmol/kg (the highest dose administered) had the greatest effect, but the dose was not high enough to elicit full therapeutic efficacy. OLP-1002R inhibited expression of $Na_v1.7$ protein in these animals, most notably at 1 fmol/kg, and decreased SCN9A mRNA expression by approximately 40% at 1 to 30 fmol/kg. The observed inhibitions were largely consistent with the in vivo therapeutic activity findings.

Taking all the in vivo and ex vivo findings together, OLP-1002R was concluded to inhibit neuropathic allodynia by inhibiting the expression of the SCN9A mRNA and the $Na_v1.7$ protein.

1.3. Summary of Safety Pharmacology

In vitro, OLP-1002 did not inhibit the human ether-à-go-go-related gene (hERG) channel current expressed in human embryonic kidney (HEK) cells at the highest concentration tested 2 μM (the limit of the validated analytical method for OLP-1002).

In the in vivo safety pharmacology studies, OLP-1002 SC administered at dose levels up to 100 nmol/kg had no effect on body temperature, neurological function, or respiratory function in rats, and had no significant toxic effect on cardiovascular function in cynomolgus monkeys.

1.4. Summary of Toxicology

In rats, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included pigment accumulation in the kidney of males administered 100 nmol/kg/dose and females administered ≥ 10 nmol/kg/dose, foreign material and vacuolated macrophage infiltrates in males and/or females administered ≥ 1 nmol/kg/dose, and an increased incidence and/or severity of mononuclear cell infiltrates at the injection sites in males and/or females administered ≥ 10 nmol/kg/dose. These findings persisted through the recovery phase in animals administered 100 nmol/kg/dose. However, the effects were considered non-adverse due to their mild severity and lack of impact on animal health and wellbeing. The no-observed-adverse-effect level (NOAEL) was 100 nmol/kg/dose. This dose level corresponded to maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from 0 to 24 hours postdose (AUC_{0-24}) values of 27.6 ng/mL and 174 ng·hr/mL, respectively, in males and 24.9 ng/mL and 128 ng·hr/mL, respectively, in females on Day 88 of the dosing phase.

In cynomolgus monkeys, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included mononuclear cell infiltrates at the SC injection sites of animals administered ≥ 10 nmol/kg/dose. This finding was not resolved with the completion of the recovery phase. However, the effects of 100 nmol/kg/dose were considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing. The NOAEL was 100 nmol/kg/dose (equivalent to 462.29 μg/kg/dose), which corresponded to C_{max} and AUC from 0 to 72 hours postdose (AUC_{0-72}) values of 121 ng/mL and 2840 ng·hr/mL in males, respectively, and 216 ng/mL and 4840 ng·hr/mL in females, respectively, on Day 88 of the dosing phase.

The genotoxic and mutagenic potential of OLP-1002 was evaluated with standard Good Laboratory Practice (GLP) via in vitro bacterial mutagenicity and chromosomal aberration studies, and was found to be negative.

1.5. Summary of Nonclinical Pharmacokinetics

In rats, following a single SC dose of ^{14}C-OLP-1002, the time of maximum observed concentration (T_{max}) was 0.5 to 1 hour for both radioactivity and parent compound. Plasma concentrations of total radioactivity were quantifiable through the last sampling time of 72 hours postdose, but was variable for the parent compound. The elimination half-life ($t_{1/2}$) of total radioactivity from plasma was 23 hours. Total radioactivity distributed into tissues, including those of the CNS protected by the blood-brain barrier. ^{14}C-OLP-1002-derived total radioactivity was not rapidly excreted from rats, with minimal amounts present in urine and feces. The bulk of the total radioactivity remained in carcasses, primarily in kidneys (cortex and medulla) and liver. Parent ^{14}C-OLP-1002 was present in plasma and tissues, but concentrations declined over time and were substantially lower than total radioactivity concentrations at the later sampling times.

After a single SC administration of ^{14}C-OLP-1002 to rats, the highest concentrations of total radioactivity were retained predominantly in the liver (10.4% to 13.3% of the dose), kidney cortex (3.47% to 4.96%), and kidney medulla (1.10% to 1.59% of the dose) through 168 hours postdose. For all other tissues, the total amounts of total radioactivity were substantially less, ranging from 0.0000203% in the 5th DRG to 0.327% in the spleen. Radioactivity was excreted slowly via both the renal and fecal routes of elimination. Total average recoveries of radioactivity in urine and feces through 336 hours postdose accounted for 2.31% and 1.75% of the administered radioactivity, respectively. The bulk of the administered total radioactivity was retained in the rat carcasses through 168, 336, 504, and 840 hours postdose. The kidney cortex, kidney medulla, and liver were the 3 tissues that retained the greatest amounts of the administered radioactivity.

Following a 16.1-µg/kg dose in rats, the plasma concentrations were still quantifiable at 72 hours postdose and the rate of elimination was slow, with $t_{1/2}$ 17.5 hours. It was not possible to accurately define the elimination phase for the 2.67- and 5.28-µg/kg dose levels.

In cynomolgus monkeys, following a single SC dose of ^{14}C-OLP-1002, T_{max} ranged from 0.25 to 1 hour for both total radioactivity and parent compound. Concentrations of total radioactivity were sustained in blood and plasma through the last sampling time of 144 hours postdose. Concentrations of parent compound were sustained in plasma through the last sampling time of 144 hours postdose in 2 of 3 monkeys, and were similar to plasma total radioactivity concentrations at 8 hours postdose. From 24 to 144 hours postdose, plasma concentrations of total radioactivity were substantially higher than for parent ^{14}C-OLP-1002 plasma concentrations.

The mean C_{max} of parent ^{14}C-OLP-1002 in plasma was 1.96 ng/mL. The mean plasma T_{max} was 0.833 hours. Plasma exposure of parent ^{14}C-OLP-1002 based on AUC extrapolated to infinity ($AUC_{0-\infty}$), was 12.7 ng·h/mL. After reaching C_{max}, plasma concentrations of parent ^{14}C-OLP-1002 declined with a mean $t_{1/2}$ of 84 hours.

1.6. Study Rationale

This is the first time OLP-1002 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data when OLP-1002 is administered SC as single and multiple doses to healthy subjects. This information, together with the pharmacodynamic (PD) and pharmacokinetic (PK) data, will help establish the doses and dosing regimen suitable for future studies in patients. The analgesic effects of OLP-1002 on a capsaicin-induced pain model will also be investigated.

1.7. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. For subjects in the PD assessment groups in Part A there will be some additional discomfort from the capsaicin test. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with OLP-1002 may be found in the Investigator's Brochure[4].

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is to assess the safety and tolerability of single and multiple SC doses of OLP-1002 in healthy subjects.

The exploratory objectives of the study are to evaluate the PD effect of OLP-1002 following single SC doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of single SC doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- incidence and severity of AEs
- vital signs measurements (blood pressure, pulse rate, respiratory rate)
- 12-lead electrocardiogram (ECG) parameters
- incidence of clinical laboratory abnormalities, based on clinical chemistry, hematology, and urinalysis test results
- physical examinations
- injection site assessment.

- demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.

2.2.2. Exploratory Endpoints

The following exploratory objectives will be assessed:

- pain intensity and duration will be assessed by AUC, maximum pain intensity (E_{max}), and time of maximum pain intensity (tE_{max}), calculated using a capsaicin-evoked pain model. The exploratory endpoint of secondary hyperalgesia will be assessed by the area of secondary area of hyperalgesia (Part A only).
- continuous (24-hour) ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval (Part A).
- heat pain threshold measurements and heat pain tolerance measurements.
- For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:

  Primary PK

  - area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])
  - AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)
  - maximum observed plasma concentration (C_{max}) (actual and DN)

  Secondary PK

  - time of the maximum observed plasma concentration (t_{max})
  - apparent plasma terminal elimination half-life ($t_{1/2}$)
- For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:

  Primary PK:

  - AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)
  - $AUC_{0-\infty}$ (actual and DN)
  - C_{max} (actual and DN)

  Secondary PK

  - minimum observed plasma concentration (C_{min})
  - t_{max}
  - $t_{1/2}$
  - observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)
  - observed accumulation ratio based on C_{max} (RAC_{max}).
  - Temporal change parameter (TCP)

Other PK parameters may also be added if deemed necessary.

3. INVESTIGATIONAL PLAN

This will be a double-blind, randomized, placebo-controlled, single and multiple SC dose study conducted in 2 parts.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, PK, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

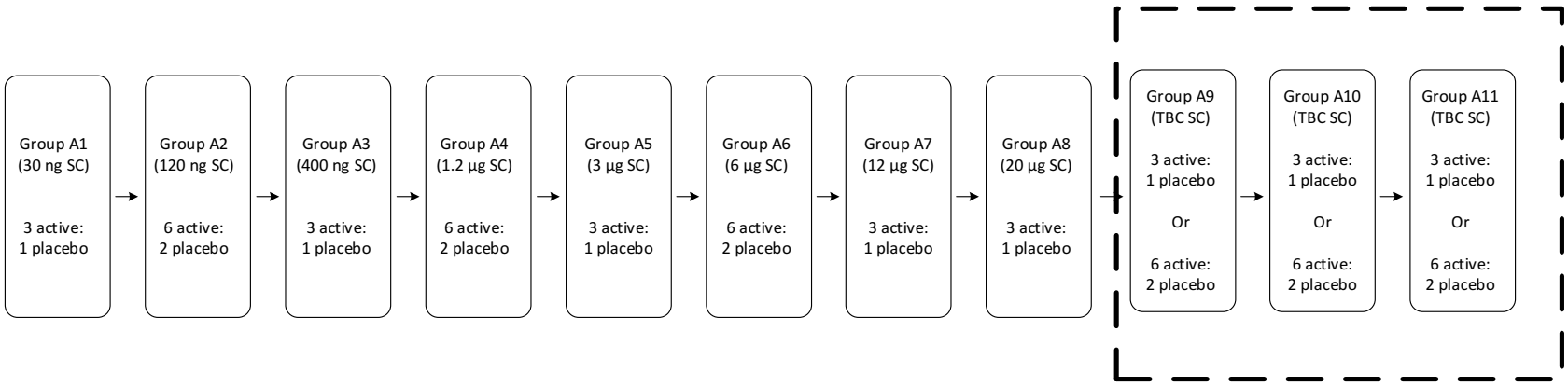
Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 10 (216 hours postdose) from the lower dose levels. For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.

In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, and A6 will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.

Sentinel dosing will be employed for all groups in Part A. To maintain the blind in a 4-subject group, the first subject will be dosed 48 hours before the second subject, and the second subject will be dosed 48 hours prior to the third and fourth subjects. In PD assessment groups, 2 subjects (1 active: 1 placebo) will be dosed 48 hours before the remaining 6 subjects (5 active: 1 placebo).

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic (Part A)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
Groups A9 to A11 may be included if required; dose levels will not exceed the maximum proposed dose of 20 µg.
Three groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

3.1.2. Part B

Part B will comprise a multiple-dose, sequential-group study. Overall, 24 subjects will be studied in 3 groups (Groups B1 to B3), with each group consisting of 8 subjects. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety and tolerability (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15.

All subjects will return for non-residential visits on Days 18 (± 2 days), 22 (± 2 days), 25 (± 2 days), and 29 (± 2 days), and for a poststudy visit on Day 57 (± 2 days).

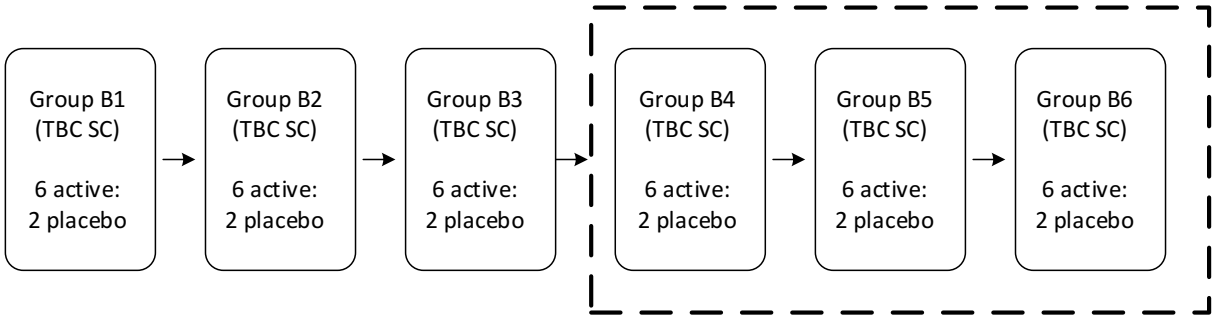
In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from the lower dose levels. Part B may start after a review of the safety, tolerability, and available PK for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

An overview of the study design is shown in Figure 2.

Figure 2: Study Schematic (Part B)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
All doses will be confirmed based on results of Part A; dose levels will not exceed the maximum proposed dose of 20 µg..
Groups B4 to B6 will be included if required.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 12 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Start of Study and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, PK, and PD data (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7]), additional dose groups may be added to the study. The maximum dose for any additional group will not exceed 20 µg. Up to 3 further groups of 8 subjects (6 active: 2 placebo) may be included in Part A, and up to 3 additional groups of 8 subjects (6 active: 2 placebo) may be included in Part B. The requirement for additional groups will be agreed with the Sponsor and documented in the Trial Master File (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential-group, ascending-dose design has been chosen for safety reasons as OLP-1002 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Subcutaneous doses have been chosen for both parts of the study, as this is the intended clinical route of administration.

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety,

tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.

This study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Continuous ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing in Part A for groups consisting of 4 subjects will be such that there will be 48 hours between the first and second subjects, and 48 hours between the second and remaining 2 subjects in each group. For groups in Part A consisting of 8 subjects, 2 subjects (1 active: 1 placebo) will be dosed 48 hours prior to the remaining 6 subjects.

In Part B, sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.

In Parts A and B, there will be a minimum interval of a 10-minute gap between dosing subjects (when dosed on the same day). Continuation to dose the remaining subjects in a group will be at the Investigator's discretion.

3.4.2. Pharmacodynamic Assessment

Pharmacodynamic assessments will be conducted for subjects in Groups A2, A4, and A6.

Human experimental pain models using healthy volunteers can be used to assess the effect of a drug or treatment under controlled clinical conditions. Capsaicin is a vanilloid responsible for the pungent taste of hot peppers. In mammalian species, capsaicin-induced pain is mediated through Group C nerve fibers following activation of vanilloid 1 transient receptor potential (TRPV1) channels[5]. $Na_v1.7$ has been implicated in controlling neuropeptide release from C-fibers, and suppression of capsaicin-induced neurogenic flair has been demonstrated by an $NA_v1.7$ inhibitor[6].

Several studies have used intradermal capsaicin for human experimental pain studies[7,8]. It has been possible to demonstrate dose-dependent responses, with intradermal injections of 100 µg generally agreed to be the ideal dosage for these studies. Intradermal injection of capsaicin causes a brief stinging/burning pain at the injection site (spontaneous pain) followed by development of secondary hyperalgesia, which can be assessed using equipment such as Von Frey hairs. A study by Gazerani et al.[5] found that the response was site-specific and while peak pain intensity and duration were greatest in the forehead it was found that areas of visible flare and secondary hyperalgesia were significantly larger in the forearm, making the forearm the most suitable site for experimentation.

Covance CRU, Leeds, UK in 2009 performed a validation study using intradermal capsaicin (Covance CRU Study: 9999-004) with between-subject and within-subject variability demonstrating that the assessments can be reliably conducted to assess pharmacological response.

For these reasons, it has been decided to:

- Measure both capsaicin-evoked pain and secondary hyperalgesia.
- Limit the number of capsaicin tests to 3 for each subject (pre-screening, baseline, and 48 hours postdose)
- Exclude subjects who have pain <3 or >9 (using a Visual Analogic Scale [VAS]) at the pre-screening visit from PD assessment groups.

3.5. Selection of Doses in the Study

3.5.1. Starting Dose

The rat has been identified as the most sensitive species in a 13-week SC toxicity study with a 4-week recovery phase (Covance study no. 8355564). The NOAEL was the 100 nmol/kg/dose (462.29 µg/kg/dose). This dose level resulted in C_{max} of 27.6 ng/mL and 24.9 ng/mL in males and females, respectively, and AUC_{0-24} of 174 ng.h/mL and 128 ng.h/mL in males and females, respectively[4]. As the exposure was lower in the female rats these data have been used to calculate the safety margins.

The dose of 462.29 µg/kg/dose corresponds to human equivalent doses (HEDs) of 74.8 µg/kg/dose, which gives a maximum recommended starting dose (MRSD) of 444 µg for a 60-kg human and thus a 15000-fold safety margin to the proposed starting dose of 30 ng and 22-fold margin to the proposed maximum dose of 20 µg. Additionally the NOAEL dose in the cynomolgus monkey was identified as 100 nmol/kg/dose (462.29 µg/kg/dose), which gives a higher HED of 150 µg/kg/dose.

In vivo, doses of 10 pmol/kg/dose (0.0462µg/kg/dose) or less were found to inhibit peripheral acute inflammatory pain. The equivalent human dose for a 60-kg human is 44 ng, thus a dose at which minimal biological effect is anticipated has been selected as the starting dose of 30 ng.

3.5.2. Exposure

Human exposures have been estimated from the pharmacokinetics in the cynomolgus monkey since a non-human primate represents the most closely related species. Approximately dose-proportional exposure was seen in the 13-week toxicity study (Covance study no. 8355565) and ^{14}C pharmacokinetic study (Covance study no. 8355568) over a dose range of approximately 1.1 to 100 nmol/kg (5.06 to 462.29 µg/kg)[4]. However, the lowest dose (5.06 µg/kg) from the ^{14}C study has been used to estimate the human exposures as it is closest to the proposed human dose range and has the sufficient quantifiable data.

The assumptions made in the human exposure estimation were that human exposure would be similar to the cynomolgus monkey and that exposure would be linear with dose. Following a dose of 5.06 µg/kg in the cynomolgus monkey, the C_{max} was 1.96 ng/mL and $AUC_{0-\infty}$ was 12.7 ng.h/mL. The extrapolated exposures at the planned human doses are shown in Table 1 with margins calculated to the exposures at the NOAEL in the female rat.

Table 1: Estimated Human Exposure and Safety Margins to the NOAEL in the Female Rat for Single Dose Administration of OLP-1002

Human dose		Single dose to human		Safety margins for single dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\infty}$
0.03	0.000500	0.000194	0.00125	129000	102000
0.12	0.00200	0.000775	0.00502	32100	25500
0.4	0.00667	0.00258	0.0167	9640	7650
1.2	0.0200	0.0077	0.0502	3210	2550
3	0.0500	0.0194	0.125	1290	1020
6	0.100	0.0387	0.251	643	510
12	0.200	0.0775	0.502	321	255
20	0.333	0.129	0.837	193	153

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

The dosing interval currently anticipated for the multiple-ascending-dose part of this study is 72 hours or 96 hours. Thus the average dosing interval (82 hours) is similar to the half-life determined in the monkey ^{14}C study of 84 hours. Dosing at approximately once per half-life would be anticipated to result in accumulation of around 2-fold. However, higher levels of accumulation were observed (2.28-fold for C_{max} and 3.76-fold for AUC_{0-24}) on Day 88 at the top dose group (100 nmol/kg, 462.28 µg/kg) in the 13-week cynomologus monkey toxicity study following twice-weekly dosing (every 72 or 96 hours). Calculations were performed to estimate the likely human half-life using a standard 1-point allometric approach from the ^{14}C cynomolgus monkey pharmacokinetic study data. The exponents used were 0.75 for apparent total plasma clearance (CL/F) and 1 for apparent volume of distribution (V_z/F) values combined with the average body weight of the animal (3.1 kg) and scaling to a 60 kg human [9–11]. This resulted in a human half-life estimate of 180 h which in turn gave an accumulation estimate of 3.7-fold based upon a dosing interval of 82 h. This further supports the use of the greater than 2-fold accumulation from the 13-week cynomolgus study to estimate exposure following multiple dosing. Multiplication of the exposure estimates for the single ascending

dose by 2.28 for C_{max} and 3.76 for AUC resulted in exposure estimates for multiple dosing presented in Table 2.

Table 2: Estimated Human Exposure and Safety Margin to the NOAEL in the Female Rat for Multiple Dose Administration of OLP-1002

Human dose		Multiple dose to human		Safety margins for multiple dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\tau,ss}$
0.03	0.000500	0.000442	0.00472	56000	27000
0.12	0.00200	0.00177	0.0189	14100	6800
0.4	0.00667	0.00589	0.0629	4230	2030
1.2	0.0200	0.017663	0.189	1410	680
3	0.0500	0.0442	0.472	560	270
6	0.100	0.0883	0.944	282	136
12	0.200	0.177	1.89	141	68
20	0.333	0.294	3.15	85	41
30	0.500	0.442	4.72	56	27

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

3.5.3. Proposed Doses

The proposed IMP dose levels for Parts A and B are shown in Table 3.

Table 3: Proposed Investigational Medicinal Product Dose Levels for Parts A and B

Study Part	Group	Dose (OLP-1002)
Part A	A1	30 ng or placebo
	A2	120 ng or placebo
	A3	400 ng or placebo
	A4	1.2 µg or placebo
	A5	3 µg or placebo
	A6	6 µg or placebo
	A7	12 µg or placebo
	A8	20 µg or placebo
	A9*	TBC or placebo
	A10*	TBC or placebo
	A11*	TBC or placebo
Part B	B1	TBC or placebo
	B2	TBC or placebo
	B3	TBC or placebo
	B4*	TBC or placebo
	B5*	TBC or placebo
	B6*	TBC or placebo

Abbreviations: TBC = to be confirmed
* groups to be included if required.

In Parts A and B, there should not be an increase of > 3-fold between dose levels above 120 ng.

For Part B, dose levels, dosing frequency, and dosing duration will be decided, in consultation with the Sponsor, on the basis of data from Part A of the study. Since predictions of human exposure of OLP-1002 suggest that OLP-1002 concentrations may be not be quantifiable and human data have been estimated from a single species, it is proposed that the highest dose in the multiple-ascending-dose part will be up to 50% of the highest dose in the single-ascending-dose part (ie, if the highest dose in the single-ascending-dose part is 20 µg, the highest dose in the multiple-ascending-dose part will be 10 µg). Therefore, if the predicted accumulation of 3.7-fold occurs, the highest exposure in the multiple-ascending-dose part will not exceed ~2-fold the maximum exposure in the single-ascending-dose part.

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

3.6. Dose Escalation

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 10 (216 hours postdose) from groups that received lower doses of OLP-1002. For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of 3 or 4 subjects, respectively, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

The justification for this is as follows:

- The study drug is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.

- A minimum of 3 subjects receiving the active drug is considered sufficient to characterize the safety profile for OLP-1002.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarizing results from all available safety assessments, will be sent to the Sponsor and a dose-escalation meeting will occur prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PD data may also be reviewed on an ongoing basis. In the event of a disagreement between Sponsor and Investigator on the dose-escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- One or more subjects experience an SAE that is considered to be related to OLP-1002.
- Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase (defined as 3 times the upper limit of normal), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).

If the sponsor deems it appropriate to resume dosing after the internal safety review, it can be done after the approval of a substantial protocol amendment.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Healthy male or females of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) between 18.0 and 28.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, single 12-lead ECG (resting heart rate > 45 bpm and < 90 bpm), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening as assessed by the Investigator (or designee).
4. Willing to abide by the contraception requirements as detailed in Appendix 4.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Any of the following:
    - QTcF > 450 ms confirmed by repeat measurement.
    - QRS duration > 110 ms confirmed by repeat measurement.
    - PR interval > 220 ms confirmed by repeat measurement.
    - findings which would make QTc measurements difficult or QTc data uninterpretable.
    - history of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
4. Female subjects who are pregnant or breastfeeding.
5. History of alcoholism or drug/chemical abuse within 1 year prior to Screening.

6. Alcohol consumption of > 21 units per week for males and >14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
7. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
8. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2).
9. Active skin conditions such as dermatitis, allergy, eczema, psoriasis, or abnormal healing.
10. Tattoos, scars, or moles that in the opinion of the Investigator are likely to interfere with dosing or study assessments at any of the potential injection sites.
11. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days or 5 half-lives of the investigational product, whichever is longer, prior to Check-in.
12. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
13. Use or intend to use any prescription medications/products other than hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptive concomitant medications within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
15. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and/or Sponsor have given their prior consent.
16. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in.
17. Receipt of blood products within 60 days prior to Check-in.
18. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
19. Poor peripheral venous access.
20. Have previously completed or withdrawn from this study or any other study investigating OLP-1002, and have previously received the investigational product.
21. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
22. Part A – PD assessment groups only
    - Subjects considered non-acceptable responders to the intradermal capsaicin test at screening, defined as maximum VAS score of < 3.0 or > 9.0.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number at the time of their randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A, Subjects 101, 102, etc., in Part B Subjects 201, 202, etc.). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal, including:
    - a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),
    - severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),
    - elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),
    - QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),
    - Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),
    - Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Vials of OLP-1002 Injection Solution 100 µg/mL (1.5 mL in 5-mL vials) and the Diluent for OLP-1002 Injection Solution (5 mL in 10-mL vials) will be supplied by the Sponsor, along with the batch/lot number and Certificate of Analysis. The Diluent for OLP-1002 Injection Solution will also be used as the Placebo formulation. A certificate of batch certification and release, authorized by a Qualified Person in the European Union (EU) will also be issued, by a Covance CRU Qualified Person, for each batch of IMP imported into the EU.

The IMPs will be stored according to the instructions on the label at the CRU in a location that is locked with restricted access.

Dose solutions (OLP-1002 Injection Solution diluted with the Diluent for OLP-1002 Injection Solution) will be prepared by Covance CRU Pharmacy staff in accordance with instructions provided in the Pharmacy Manual. The Placebo formulation will be the Diluent for OLP-1002 Injection Solution without further manipulation.

5.2. Study Treatment Administration

Subjects will be administered the IMP in numerical order. OLP-1002 will be administered by SC injection in the upper arm. If subcutaneous dosing of OLP-1002 in the upper arm is not possible, the subject may be dosed in the abdomen at the Investigator's discretion. For subjects in Groups A2, A4, and A6, dosing will be on the opposite arm to the intradermal capsaicin test.

5.3. Randomization

The randomization code will be produced by the statistics department at Covance using a computer-generated pseudo-random permutation procedure. In Part A, 1 subject in groups

consisting of 4 subjects, and 2 subjects in groups consisting of 8 subjects, will be randomly assigned to receive placebo. In Part B, 2 subjects per group will be randomly assigned to receive placebo. All other subjects in a group will be randomized to receive OLP-1002.

Prior to the start of the study, a copy of the master randomization code will be supplied into the Covance CRU pharmacy staff (in sealed envelopes).

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo solution will be identical in appearance to the OLP-1002.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

To maintain the blind, the Investigator will be provided with sealed randomization code-break envelopes for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose-escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

All doses of IMP will be administered by suitably qualified study site staff.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription medications/products from 14 days prior to dosing until the Follow-up visit, and non-prescription medications/products from 7 days prior to dosing until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests. On dosing days, subjects will receive a light breakfast approximately 2 hours prior to dosing. Meals will be provided as appropriate at other times and water will be freely available at all times.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until the Follow-up visit.

Xanthine-containing foods and beverages will not be allowed from 36 hours before Check-in until Discharge from the site. Xanthine-containing foods and beverages will also not be allowed form 36 hours before non-residential site visits.

Chili pepper/hot sauce will not be allowed for 48 hours prior to Check-in for all subjects. Subjects in Groups A2, A4, and A6 will not be allowed chili pepper/hot sauce for 48 hours prior to their pre-screening visit.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until Discharge. Following discharge, up to 2 units/day of alcohol are permitted until 36 hours before each non-residential visit and the Follow-up visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 3 days before Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during this

time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit. Subjects should not be in receipt of blood products for 60 days prior to check-in.

6.6. Other Restrictions

Subjects in Groups A2, A4, and A6 will not be allowed to shower within 1 hour prior to the capsaicin-evoked pain tests at prescreening, predose, and postdose.

Subjects will not be allowed to apply moisturizing creams or oils to the dosing site within 1 hour prior to dosing, or to the assessment site within 1 hour prior to the capsaicin-evoked pain test.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- vital signs
- blood samples
- cardiac monitoring/ECG extractions
- any other procedures.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, PK analysis will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the

event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Pharmacodynamic Assessments

Capsaicin intradermal test will be performed for subjects in Groups A2, A4, and A6. Each subject will be tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).

7.2.1. Capsaicin-evoked Pain Model

The capsaicin model will be conducted by intradermal injection of capsaicin (100 µg in 100 µL of sterile saline containing 8% [w/w] Tween 80) into the skin of the anterior aspect of the forearm, midway between the elbow and the wrist. The bleb area (wheal) will be a sign of local plasma extravasation. An assessment of the pain intensity related to capsaicin injection will be estimated by repeated use of a VAS from injection to 5 minutes post-injection or until the pain intensity returned to zero. The AUC, E_{max}, and tE_{max} will be calculated and reported using dedicated software.

7.2.2. Secondary Hyperalgesia

The area of secondary hyperalgesia will be quantified with a 60-g weighted von Frey hair, by stimulating along 8 linear paths (4 vectors crossing at the location of the injection site) arranged vertically and horizontally around the stimulation site in 5-mm steps (starting approximately 6 cm away from the injection site). The area of secondary hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection.

7.3. Safety and Tolerability Assessments

Safety and tolerability assessments will be conducted at the times indicated in the Schedule of Assessments (Appendix 6). Timepoints may be adjusted based on an ongoing review of the data, and additional assessments may be conducted if deemed necessary by the Investigator or designee.

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked

about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a follicle-stimulating hormone (FSH) test and pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

Subjects must be supine for at least 5 minutes before blood pressure, pulse rate, and respiratory rate measurements.

7.3.4. Electrocardiogram

7.3.4.1. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value > 500 msec
- QTcF change from the mean baseline (Day 1 predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.4.2. Continuous (24-hour) Electrocardiogram

At the times indicated in the Schedule of Assessments (Appendix 6), continuous (24-hour) ECGs will be performed.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint. Each extraction will last for 5 minutes. Environmental distractions (eg, television, playing games, radio, conversation) should be avoided during the pre-ECG time window.

Continuous 24-hour ECGs are not planned for Part B of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.3.5. Heat Pain Threshold Test

Heat pain threshold tests will be conducted at the times indicated in the Schedule of Assessments (Appendix 6).

A computer-controlled thermal sensory analyzer device will be used to measure the heat pain threshold and tolerance level of the subjects. The heat pain assessments will be conducted on the subject's thigh.

Heat Pain Threshold:

For heat pain threshold measurements, the thermode will be placed directly on the skin of the right thigh, within an area selected before the start of the experiment and defined by surgical marking. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in

their dominant hand, to indicate when the heat pain threshold (first sensation of heat pain) is reached by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Heat Pain Tolerance:

For heat pain tolerance measurements, the thermode will be placed within the same surgically marked skin area of the anterior side of the right thigh, which was used to assess heat pain threshold. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in their dominant hand, to indicate when the heat-evoked pain has reached an intensity that is no longer tolerable, by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Safety Precautions

As there is a risk that OLP-1002 may affect the heat pain threshold, Covance CRU will put appropriate safety measures in place to ensure that subjects are not exposed to extremes of temperature when taking a shower or consuming hot drinks. During the heat pain safety assessments, the cut-off temperature for either test is 53 °C in order to prevent skin injury.

7.3.6. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

7.3.7. Body Weight and Height

Body weight (in underclothes) and height will be recorded at the times indicated in the Schedule of Assessments in Appendix 6. BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{body weight (kg)}}{(\text{height [m]})^2} \quad (\text{kg/m}^2)$$

7.3.8. Injection Site Assessments

Injection site assessments will be made at the times indicated in the Study Plan (Appendix 6).

Assessments will involve evaluation of the dosing site for the following criteria:

- Pain will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4

None	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Requires medical intervention greater than analgesia

• Redness will be assessed by estimating the size of the red patch at the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm	51-100 mm	More than 100 mm	Requires medical intervention greater than analgesia

• Swelling will be assessed by estimating the size of the raised area around the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm and does not interfere with activity	51-100 mm or interferes with activity	More than 100 mm and prevents daily activity	Requires medical intervention greater than analgesia

In addition, how the swelling affects the subject in their daily routing activities will be considered.

• Tenderness will be evaluated using the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Mild pain to touch	Moderate Pain to touch	Severe pain to touch	Requires medical intervention

				greater than analgesia

- Bruising and ulceration will be evaluated as being present or absent.

Local tolerability ratings of ≥Grade 3 and the presence of ulceration will be recorded as an adverse event.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. In order to achieve PD endpoints in Part A, additional subjects will be included in 3 groups (8 subjects in total; 6 active: 2 placebo). Up to 3 additional groups may be added to Part A, consisting of either 4 subjects (3 active; 1 placebo) or 8 subjects (6 active; 2 placebo). Up to 3 additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.2. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

8.4. Pharmacodynamic Analyses

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned.

8.5. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- Mild: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but posing no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- Not Related: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- Unlikely Related: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- Related: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at the Follow-up visit will be followed up, where possible,

until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit (CRU). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Covance Drug Safety Services (DSS) Europe, Maidenhead, UK are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to DSS and the Sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Covance DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 2 working days of the initial notification to DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy reported by female subjects or

the female partners of male subjects should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total protein Urea	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[a]:	**Drug screen[b]:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test MDMA Alcohol breath test	Follicle-stimulating hormone[a] Serum pregnancy test (human chorionic gonadotropin)[a] Urine pregnancy test[c]

[a] Only analyzed at Screening.
[b] Only analyzed at Screening and Check-in.
[c] A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	19	76
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			109.5

Part B

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	29	116
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			194.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject during the study will not exceed that donated during a standard blood donation (approximately 500 mL).

Appendix 4: Contraception Guidance

Definitions

Females of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Females of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary highly effective and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary highly effective methods of contraception include:

- surgical method performed at least 3 months prior to the Screening visit:
  - bilateral tubal ligation
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)
- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects can only choose a cervical cap or diaphragm if they have already had a prescription and fitting by their healthcare provider to ensure protocol requirements are met. Female subjects of childbearing potential should refrain from donation of ova from Check-in until 90 days after the Follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide
- vasectomised male subject (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success).

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the Follow-up visit.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the Follow-up visit.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a

public registry, all identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled and randomized subject, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

Study Plan – Part A (Single Dose)

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Urine drugs of abuse screen		X	X							
Alcohol breath test		X	X							
Cotinine test		X	X							
Serology		X								
Hormone panel		X								
Urine pregnancy test[a]		X	X							X
Informed consent	X	X								
Study residency:										
Check-in			X							
Check-out					Day 3 (48 hours postdose)					
Non-residential visit	X	X				X	X	X	X	X
Study drug administration:					Day 1 (0 hours)					
Safety and tolerability:										
Adverse event recording		X	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording		X	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature		X			Predose, 1, 2, 4, 8, 24 (± 1 hour), and 48 hours postdose	X	X	X	X	X

	Pre-screening[d]	**Screening**	**Day -2**	**Day -1**	**Days 1 to 3**	**Day 4**	**Day 7 (± 2 days)**	**Day 10 (± 2 days)**	**Day 14 (± 2 days)**	**Poststudy (Day 28 ± 2 days)**
Supine 12-lead ECG		X			Predose, 4, 24 (± 1 hour) and 48 hours postdose		X		X	X
Continuous ECG extraction[b,c]				-24, -23.5, -23, -22.5, -22, -21.5, -21, -20, -18, -16, -12 hours	Day 1: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours					
Heat pain threshold test (heat pain threshold and heat pain tolerance)					Day 1: predose, 2, 4, 12, and 24 hours postdose (± 1 hour)					
Clinical chemistry, haematology, and urinalysis		X			48 hours postdose		X		X	X
Height and BMI		X								
Body weight		X	X							X
Physical examination		X								
Symptom-directed physical examination					Prior to discharge		X		X	X

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Injection site assessment					Predose, 1, 2, 4, 8, 24, 48 hours postdose		X		X	X
Pharmacokinetics[e]										
Blood sampling					Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose	X	X	X	X	X
Pharmacodynamics[d]:										
Intradermal capsaicin test (capsaicin-evoked pain and secondary hyperalgesia measurement)	X		X		Day 2 (The area of secondary area of hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection)					

Abbreviations: BMI = body mass index; ECG = electrocardiogram.
[a] A positive urine pregnancy test result will be confirmed with a serum pregnancy test.
[b] All times are relative to dosing with OLP-1002.
[c] Continuous ECG recording may begin at approximately 25 hours before dosing to allow for checks to be completed prior to the first extraction timepoint and will continue for 24 hours postdose, ie, until after the last timepoint for ECG extraction (24 hours postdose). At timepoints for ECG extractions, subjects will be supinely resting for a total of 15 minutes (10-minute supine rest period, 5-minute extraction). Data will be archived for potential future analysis and will not be available for review during the study.
[d] Pharmacodynamic assessment groups only.
[e] PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

Study Plan – Part B (Multiple Dose)

	Screening	Day -1	Days 1-15	Day 18 (± 2 days)	Day 22 (± 2 days)	Day 25 (± 2 days)	Day 29 (± 2 days)	Poststudy (Day 57 ± 2 days)
Inclusion/exclusion criteria	X							
Demographic data	X							
Medical history	X							
Urine drugs of abuse screen	X	X						
Alcohol breath test	X	X						
Cotinine test	X	X						
Serology	X							
Hormone panel	X							
Urine pregnancy test[a]	X	X			X		X	X
Informed consent	X							
Study residency:								
Check-in		X						
Check-out			Day 15 (48 hours postdose)					
Non-residential visit	X			X	X	X	X	X
Study drug administration:			Days 1, 4, 7, 10, and 13					
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature	X		Day 1: predose, 1, 2, 4 and 8 hours postdose Day 2, Day 4 (postdose), Day 5, Day 7 (postdose), Day 9, Day 10 (postdose), Day 12, Day 13: predose, 1, 2, 4 and 8 hours postdose, and Day 15	X	X	X	X	X

	Screening	Day -1	Days 1-15	Day 18	Day 22	Day 25	Day 29	Poststudy (Day 57 ± 2 days)
Heat pain threshold test (heat pain threshold and heat pain tolerance)	X		Day 1 and Day 13: predose, 1, 2, 4, 8, 24 hours postdose					
Supine 12-lead ECG	X		Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Clinical chemistry, haematology, and urinalysis	X	X	Days 2, 5, 9, 12, 17		X		X	X
Height and BMI	X							
Body weight	X	X						X
Physical examination	X							
Symptom-directed physical examination			Days 1, 4, 7, 10, 13		X		X	X
Injection site assessment			Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Pharmacokinetics:								
Blood sampling[b]			Day 1 and Day 13: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose Days 4, 7, 10 Predose Day 15	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram.
[a] Positive urine pregnancy test results will be confirmed with a serum pregnancy test.
[b] PK timepoints will be reviewed based on emerging data and may be updated.

Appendix 7: Protocol Amendment Summary of Changes

Protocol Amendment 2 (Version 2.1; 21 November 2018)

This non-substantial amendment has been issued to correct minor inconsistencies in PK sampling timepoints, data cut off for dose escalation, clinical laboratory assessment timepoints, and the synopsis. Additionally, details of the injection site assessments have been added to the protocol.

A detailed summary of changes is presented below. For each section, deleted text is shown in ~~strikethrough~~, and new text is shown in **bold**:

Synopsis: Endpoints

Text added:

Safety:
Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, **heat pain threshold and tolerance,** and physical examinations.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from groups that received lower doses of OLP-1002.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day **10** (**216** hours postdose) from groups that received lower doses of OLP-1002.

Section 7.3.8

Entire section added to describe injection site assessments.

Appendix 3

Total blood volume for PK analysis (76 mL) added.

Appendix 6 - Schedule of assessments Part A

24 hour postdose continuous ECG recording timepoint added.

Appendix 6 - Schedule of assessments Part B

Clinical chemistry, haematology, and urinalysis for Days 1-15 previously read:

Days 2, ~~4~~, ~~7~~, ~~10~~,~~13~~

Clinical chemistry, haematology, and urinalysis for Days 1-15 now reads:

Days 2**, 5, 9, 12, 17**

PK blood sampling for Days 1-15 previously read:

Day 1 and Day ~~15~~: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, ~~8,~~ ~~11, 15~~ Predose

PK blood sampling for Days 1-15 now reads:

Day 1 and Day **13**: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose
Days 4, **7, 10** Predose
Day 15

Protocol Amendment 1 (Version 2; 02 October 2018)

This amendment has been generated following the non-acceptance of the original protocol (version 1) by the Medicines and Healthcare products Regulatory Agency (MHRA) on 20 September 2018. All changes made have been in response to comments provided by the MHRA.

The primary changes in this amendment are:

1. Inclusion of PK sampling in Parts A and B:
    - PK objective and exploratory endpoints added (Section 2).
    - Discussion of PK included Section 3.4.
    - PK stopping criteria added to Section 3.7.
    - PK assessments included in Section 7.1.
    - PK population and analysis (Section 8.2.1).
    - Blood volumes updated to include samples for PK assessments (Appendix 3).
2. Exclusion and stopping criteria updated
    - Women who are pregnant or breastfeeding have been excluded from the study (Section 4.2).
    - Liver function tests, tachycardia, and hypertension stopping criteria have been updated (Section 3.7 and Section 4.4).
    - Stopping criteria for SAEs and serious AEs have been added (Section 3.7 and Section 4.4).
3. Safety, tolerability, and PK data up to Day 22 in Part B will be reviewed prior to dose escalation (Section 3.1.2).

4. Sentinel dosing included in Part B (Section 3.1.2).
5. It has been specified that the maximum dose for additional groups will not exceed 20 µg (Section 3.5.3).

Minor changes:

1. Additional clinical laboratory evaluations have been included on Day 14 in Part A.
2. The definition of the Safety population has been updated to include all subjects who receive OLP-1002.
3. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below. For each section, deleted text is shown in s~~trikethrough~~, and new text is shown in **bold**:

Section 1.6

Previously read:

This information, together with the pharmacodynamic (PD data, will help establish the doses and dosing regimen suitable for future studies in patients.

Now reads:

This information, together with the pharmacodynamic (PD) **and pharmacokinetic (PK)** data, will help establish the doses and dosing regimen suitable for future studies in patients.

Section 2.1

Objective added:

Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

Section 2.2.1

Endpoint added:

- **demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.**

Section 2.2.2

Endpoints added:

- **For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:**

Primary PK

- **area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])**
- **AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)**
- **maximum observed plasma concentration (C_{max}) (actual and DN)**

Secondary PK

- **time of the maximum observed plasma concentration (t_{max})**
- **apparent plasma terminal elimination half-life ($t_{1/2}$)**

- **For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:**

Primary PK

- **AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)**
- **$AUC_{0-\infty}$ (actual and DN)**
- **C_{max} (actual and DN)**

Secondary PK

- **minimum observed plasma concentration (C_{min})**
- **t_{max}**
- **$t_{1/2}$**
- **observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)**
- **observed accumulation ratio based on C_{max} (RAC_{max}).**
- **Temporal change parameter (TCP)**

Other PK parameters may also be added if deemed necessary.

Section 3.1.1

Previously read:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All

subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from the lower dose levels.

Now reads:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, **PK,** and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day **10** (**216** hours postdose) from the lower dose levels. **For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.**

Figure 1 – footnote

Text added:

Groups A9 to A11 may be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Figure 2 – footnote

Text added:

Groups B4 to B6 will be included if required**; dose levels will not exceed the**

maximum proposed dose of 20 µg.

Section 3.1.2

Previously read:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. ~~There will be no sentinel dosing in Part B.~~ For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from the lower dose levels. Part B may start after a review of the safety ~~and~~ tolerability for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Now reads:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from the lower dose levels. Part B may start after a review of the safety**,** tolerability**, and available PK data** for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Section 3.3

Previously read:

Following review of the safety, tolerability, and PD data, additional dose groups

may be added to the study.

Now reads:

Following review of the safety, tolerability, **PK,** and PD data **(where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7])**, additional dose groups may be added to the study. **The maximum dose for any additional group will not exceed 20 µg.**

Section 3.4

Previously read:

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

~~Pharmacokinetic analysis will not be conducted in this study.~~ The bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose~~s~~ would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. ~~Thus, the additional burden of sampling procedures would not be justified by the quality of the data which it would generate.~~

Now reads:

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be

reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. **Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable.** It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. **In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.**

Section 3.4.1

Previously read:

In Part B, ~~all subjects in a group will be dosed on the same day~~. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3).

Now reads:

In Part B, **sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day**. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). **If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.**

Section 3.5.3

Text added:

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be

lower than the starting dose.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of ~~5~~ subjects, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002. **For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.**

In Part B, doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. **Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.**

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of **3 or 4** subjects**, respectively**, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Section 3.7

Previously read:

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in ~~liver function tests (~~aspartate aminotransferase, alanine aminotransferase~~,~~ alkaline phosphatase

~~and total bilirubin)~~ defined as 3 times the upper limit of normal in ~~3~~ or more subjects in a group ~~(~~confirmed with repeat testing~~)~~.

- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.

Now reads:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- **One or more subjects experience an SAE that is considered to be related to OLP-1002.**
- **Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.**
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase **or** alkaline phosphatase **(**defined as 3 times the upper limit of normal**), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be** confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- **The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no**

greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).

Section 4.2

Exclusion criteria added:

4. Female subjects who are pregnant or breastfeeding.

Section 4.4

Previously read:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal

Now reads:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal**, including:**
  - **a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),**
  - **severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),**
  - **elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),**
  - **QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),**
  - **Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),**
  - **Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).**

Section 7.1

Section added:

7.1 Pharmacokinetic Assessments

7.1.1 Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment

period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, only samples collected from subjects that received >12 µg OLP-1002 will be initially analyzed. If PK data is quantifiable at concentrations of OLP-1002 >12 µg, samples from lower dose groups will be retrospectively analyzed. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2 Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

Section 8.2

Previously read:

8.2.~~1~~ Pharmacodynamic population

The PD population will include all subjects who received at least 1 dose of ~~study treatment~~ OLP-1002 or placebo and for whom PD can be evaluated.

8.2.~~2~~ Safety Population
The safety population will include all subjects who received at least 1 dose of ~~study treatment~~ or placebo ~~and have at least 1 postdose safety assessment~~.

Now reads:

8.2.1 Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.**2** Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.**3** Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3 Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma and urine concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

Appendix 3

Table updated:

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis*	**4**	**19**	**76**
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			~~33.5~~**109.5**

Part B

	Volume per blood sample (mL)	**Maximum number of blood samples**	**Total amount of blood (mL)**
Pharmacokinetic analysis	**4**	**29**	**116**
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			~~78.5~~**194.5**

Appendix 6

PK and Blood sampling rows added to the schedule of events for Part A and Part B. In the Schedule of events for Part A, footnote e was added. In the Schedule of events for Part B, footnote b was added.

Clinical chemistry, hematology, and urinalysis was added to the Schedule of events

for Part A on Day 14.

Protocol

OLP-1002 – A First-in-human, Double-blind, Placebo-controlled, Single and Multiple Subcutaneous Dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Male and Female Subjects

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Principal Investigator:
[redacted]

SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

October 02, 2018

[redacted]

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

[redacted]
Principal Investigator

30 OCT 2018
Date

STUDY IDENTIFICATION

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SYNOPSIS

Title of study: OLP-1002 – A first-in-human, double-blind, placebo-controlled, single and multiple subcutaneous dose, safety, tolerability, pharmacokinetic, and pharmacodynamic study in healthy male and female subjects
Objectives: The primary objective of the study is to assess the safety and tolerability of single and multiple subcutaneous doses of OLP-1002 in healthy subjects. The exploratory objectives of the study are to evaluate the pharmacodynamic effect of OLP-1002 following single subcutaneous doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of a single subcutaneous doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.
Study design: This will be a double-blind, randomized, placebo-controlled, single and multiple subcutaneous dose study conducted in 2 parts, including healthy male and female subjects.
Number of subjects: Part A: 44 subjects will be studied in 8 groups (5 groups of 4 and 3 groups of 8). Part B: 24 subjects will be studied in 3 groups (Groups B1 to B3). Up to 24 additional subjects may be recruited into Part A and Part B of the study if required.
Diagnosis and main criteria for inclusion: Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 28.0 kg/m^2 (inclusive).
Investigational products, dose, and mode of administration: Test product: OLP-1002 Proposed dose levels for Part A: 30 ng, 120 ng, 400 ng, 1.2 µg, 3 µg, 6 µg, 12 µg, and 20 µg. Proposed dose levels for Part B: the doses for Part B will be decided in consultation with the Sponsor and on the basis of data from Part A of the study. The highest dose in Part B will be up to 50% of the highest dose in Part A. Administration route: subcutaneous
Reference product and mode of administration: Reference product: placebo Administration route: subcutaneous
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to Follow-up): approximately 8 weeks for Part A and approximately 12 weeks for Part B.

Endpoints:

Pharmacodynamics:

In Part A, the analgesic effect of OLP-1002 will be investigated in 3 groups consisting of 8 subjects (6 active: 2 placebo) using experimental capsaicin-evoked pain methods. Measurement of capsaicin-evoked pain will be performed at pre-screening, baseline and on Day 2, and secondary hyperalgesia at 5 and 30 minutes post-capsaicin injection. Continuous electrocardiogram (ECG) recording will be conducted to investigate the effect of OLP-1002 on cardiac function.

Safety:

Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, and physical examinations.

Pharmacokinetics:

In Part A, the following PK parameters will be determined where possible: area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$), maximum observed plasma concentration (C_{max}), time of the maximum observed plasma concentration (t_{max}), and apparent plasma terminal elimination half-life ($t_{1/2}$). PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

In Part B, the following PK parameters will be determined where possible: AUC over a dosing interval ($AUC_{0-\tau}$), $AUC_{0-\infty}$, $C_{max,}$ minimum observed plasma concentration (C_{min}), t_{max}, $t_{1/2}$, observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$), observed accumulation ratio based on C_{max} (RAC_{max}), and Temporal change parameter (TCP). PK samples from all groups in Part B will be analyzed.

Statistical methods:

Pharmacodynamics:

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of pharmacodynamic data is planned.

Safety:

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

Pharmacokinetics:

Individual plasma concentrations and PK parameters of OLP-1002 will be listed and summarized using descriptive statistics. Individual and mean OLP-1002 concentration-time profiles will be presented graphically.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours postdose
BMI	body mass index
C_{max}	maximum observed plasma concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSA	clinical study agreement
DN	Dose normalized
DRG	dorsal root ganglion
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
E_{max}	maximum pain intensity
FCA	Freund's Complete Adjuvant
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SC	subcutaneous(ly)
SNL	spinal nerve ligation
$t_{1/2}$	elimination half-life
tE_{max}	time of maximum pain intensity
T_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
VAS	Visual Analogic Scale

VGSC	voltage-gated sodium channel

1. INTRODUCTION

1.1. Overview

OLP-1002 is a novel peptide nucleic acid (PNA) derivative which acts as a specific voltage-gated sodium channel (VGSC) protein ($Na_v1.7$) inhibitor, and is being developed by OliPass for the treatment of pain.

The $Na_v1.7$ protein is a subtype of VGSCs. $Na_v1.7$ is particularly important in nociception and pain signaling, with congenital loss-of-function mutations in $Na_v1.7$ resulting in the inability to experience pain. Selective $Na_v1.7$ inhibitors are believed to have the potential to treat severe pain safely[1]. The active sites of VGSC subtypes are virtually indistinguishable by their 3-dimensional structure and thus the discovery of selective $Na_v1.7$ small molecule inhibitors has been extremely challenging. Since inhibition of $Na_v1.5$ subtype elicits long QT cardiotoxicity, inhibition of $Na_v1.5$ subtype should be avoided at therapeutic doses.

To date, there are several $Na_v1.7$ inhibitors claimed to be selective that have been evaluated in human subjects:

- Vixotrigine (formerly known as raxatrigine) inhibits $Na_v1.7$ as well as other VGSC subtypes. Vixotrigine is in phase III clinical development for trigeminal neuralgia. Due to the limited $Na_v1.7$ selectivity over $Na_v1.5$, vixotrigine was evaluated primarily in patients with a low heart risk.
- Funapide is a $Na_v1.7$ inhibitor with limited $Na_v1.7$ selectivity, and was in phase IIb clinical trials as of July 2014. Although funapide showed analgesic activity in a small number of erythromelalgia patients, dose-limiting adverse events (AEs), including dizziness and somnolence, were observed[2]. The central nervous system (CNS) AEs were due to its poor $Na_v1.7$ selectivity.
- PF-05089771 is a $Na_v1.7$ selective inhibitor with a claimed $Na_v1.7$ selectivity of > 2000-fold versus other subtypes of sodium channel and was evaluated in patients of erythromelalgia or dental pain. It is thought low drug concentrations achieved in the target tissue could be a possible explanation for its poor analgesic activity in human patients[3].

OLP-1002 is fully complementary to a 14-mer RNA sequence spanning the junction of intron 4 and exon 5 in the human SCN9A pre-mRNA which codes for the $Na_v1.7$ channel. OLP-1002 yields SCN9A mRNA splice variant(s) encoding variant $Na_v1.7$ protein(s) lacking the sodium channel activity (ie, a non-functional channel), thereby inhibiting $Na_v1.7$ channel function.

1.2. Summary of Nonclinical Pharmacology

1.2.1. In Vitro Pharmacology Studies

Overall, results from the in vitro pharmacology studies showed OLP-1002 elicits responses consistent with its designed function[4]. It inhibits SCN9A mRNA expression and yields the

$Na_v1.7$ variant protein or proteins lacking sodium channel activity. Its effects are highly selective, which may provide for an improved margin of safety compared to other $Na_v1.7$ inhibitors.

OLP-1002 at 1 to 100 zM in PC3 prostate carcinoma cells induced exon skipping and yielded SCN9A mRNA splice variant(s) encoding a $Na_v1.7$ variant protein or proteins lacking sodium channel activity.

In rat dorsal root ganglion (DRG) neuronal cells, OLP-1002 at 1000 zM inhibited $Na_v1.7$ protein expression by > 50%, while OLP-1002R at 100 and 1000 zM inhibited $Na_v1.7$ expression almost completely. As OLP-1002R is fully complementary to rat SCN9A pre-mRNA, OLP-1002R would be predicted to be more potent than OLP-1002 in this cell type.

SCN9A mRNA expression level was evaluated by quantitative polymerase chain reaction (qPCR). OLP-1002 inhibited the expression of the SCN9A mRNA in PC3 cells with sub-attomolar potency.

In SH-SY5Y human neuroblastoma cells stimulated with tumor necrosis factor (TNF)-1α to upregulate the expression of SCN9A mRNA, OLP-1002 decreased expression by 46% to 49% at 1 fM to 10 pM. In rat DRG neuronal cells, OLP-1002 at 1 fM significantly decreased SCN9A mRNA expression by 54%.

In rat DRG neuronal cells, OLP-1002 markedly and significantly inhibited the sodium current by 77% at 0.1 aM and 73% at 1 aM, while for OLP-1002R, the inhibition was 66% at 0.1 aM and 70% at 1 aM. Given that rat DRG neuronal cells express various subtypes of sodium channel, the observed inhibitions of 66% to 77% correspond to the complete knockout of the $Na_v1.7$ sodium channel subtype with OLP-1002 or OLP-1002R.

The $Na_v1.7$ selectivity over $Na_v1.5$ was evaluated in H9C2 rat cardiomyocytes which are known to abundantly express the rat $Na_v1.5$ sodium channel subtype. Following incubation with OLP-1002 or OLP-1002R at 1 aM or 1 pM, there were no notable decreases in the sodium current. Considering that OLP-1002 and OLP-1002R inhibit the expression of $Na_v1.7$ protein at 1 aM or lower in rat DRG neuronal cells, the $Na_v1.7$ selectivity of OLP-1002 and OLP-1002R over $Na_v1.5$ is estimated to be in excess of one million-fold. Such a large $Na_v1.7$ selectivity over $Na_v1.5$ has not been realized with small molecule $Na_v1.7$ inhibitors, suggesting that OLP-1002 potentially offers pain management with much greater cardiovascular safety.

1.2.2. In Vivo Pharmacology Studies

Spinal nerve ligation (SNL) has been widely applied as a rat model for neuropathic pain. OLP-1002 and OLP-1002R were found to be very potent, but highly variable in potency, in reversing neuropathic allodynia in this model. Analyses of the therapeutic potency strongly suggested that a marked proportion of subcutaneously (SC) administered OLP-1002 or OLP-1002R may have been topically delivered directly to the spinal nerves exposed in the dorsal cavity created during the SNL modelling. In addition, the variability of the therapeutic potency may be due to a variable degree of healing of the SNL surgery wound. If an animal

recovers slowly, the animal tends to be left with a dorsal cavity. Therefore, estimations of potency in these studies with this model should be treated with caution.

In one study using the SNL model, allodynia in rats was slowly and gradually reversed by OLP-1002 SC administered at nominal doses of 1, 3, and 6 pmol/kg once every 2 days (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). As the onset time for pain reduction was 4 days, the doses used were not sufficient for fast onset of activity. In this study, the animals should have reasonably recovered from the dorsal wound, and therefore less susceptible to topical delivery directly to the exposed spinal nerves. However, in another study in this model, when OLP-1002 was intraperitoneally (IP) administered once every 3 days to avoid the likelihood of local delivery to the spinal nerves, OLP-1002 surprisingly reversed the allodynia at 5 fmol/kg, and was superior or comparable to pregabalin 30 mg/kg, a gold standard for neuropathic pain studies. The high potency shown at 5 fmol/kg IP strongly suggests the possibility that OLP-1002 is efficiently absorbed by the enteric nervous system, travels to the spinal cord, and then redistributes to the spinal nerves of the SNL ligation. This opens the possibility of efficient oral delivery of OLP-1002 to the spinal cord.

When evaluated for their ability to reverse the inflammatory pain in rats inflicted with Freund's Complete Adjuvant (FCA)-induced severe paw inflammation, OLP-1002 at 300 pmol/kg and OLP-1002R at 100 pmol/kg significantly reversed the thermal hyperalgesia, and both were more effective than pregabalin 30 mg/kg.

Paw burn injury induces hyperalgesia in rats and is known to upregulate $Na_v1.7$ expression in the L5 and L6 DRGs of the affected side. Burn injury induces a far weaker degree of paw inflammation than FCA-induced paw inflammation. OLP-1002 SC administered inhibited the thermal hyperalgesia in paw burn injury in a dose-dependent manner. At 25 fmol/kg, OLP-1002 did not inhibit thermal hyperalgesia. Although OLP-1002 at 625 fmol/kg significantly inhibited the thermal hyperalgesia, the efficacy was moderate and weaker than pregabalin 30 mg/kg. This suggests that SC dosing does not offer the local topical delivery to spinal nerves in this model as seen in rats without a dorsal cavity wound. In this study, the $Na_v1.7$ expression in the DRG of the burn injury side significantly decreased by 58% with 625 fmol/kg OLP-1002, validating the target engagement for analgesic activity.

An intraplantar injection of formalin induces severe acute pain. The contributors to acute pain are known to be complex and require further elucidation. However, acute peripheral inflammation is known to contribute much to Phase II Pain (pain from 10 to 40 min after the formalin injection). In this model, OLP-1002 significantly inhibited Phase II Pain at comparable or saturated efficacy when SC administered at 10 to 100 pmol/kg (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). Thus peripheral acute inflammatory pain could be treated with 10 pmol/kg or less.

1.2.3. Ex Vivo Pharmacology Studies

One day post-SC injection, OLP-1002 and OLP-1002R at 100 pmol/kg significantly inhibited the expression of $Na_v1.7$ protein by 39% and 57%, respectively, in the spinal cord of rats subjected to SNL.

In other rats subjected to SNL, OLP-1002R slowly and gradually reversed the allodynia in a dose-dependent manner. OLP-1002R at 30 fmol/kg (the highest dose administered) had the greatest effect, but the dose was not high enough to elicit full therapeutic efficacy. OLP-1002R inhibited expression of $Na_v1.7$ protein in these animals, most notably at 1 fmol/kg, and decreased SCN9A mRNA expression by approximately 40% at 1 to 30 fmol/kg. The observed inhibitions were largely consistent with the in vivo therapeutic activity findings.

Taking all the in vivo and ex vivo findings together, OLP-1002R was concluded to inhibit neuropathic allodynia by inhibiting the expression of the SCN9A mRNA and the $Na_v1.7$ protein.

1.3. Summary of Safety Pharmacology

In vitro, OLP-1002 did not inhibit the human ether-à-go-go-related gene (hERG) channel current expressed in human embryonic kidney (HEK) cells at the highest concentration tested 2 μM (the limit of the validated analytical method for OLP-1002).

In the in vivo safety pharmacology studies, OLP-1002 SC administered at dose levels up to 100 nmol/kg had no effect on body temperature, neurological function, or respiratory function in rats, and had no significant toxic effect on cardiovascular function in cynomolgus monkeys.

1.4. Summary of Toxicology

In rats, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included pigment accumulation in the kidney of males administered 100 nmol/kg/dose and females administered ≥ 10 nmol/kg/dose, foreign material and vacuolated macrophage infiltrates in males and/or females administered ≥ 1 nmol/kg/dose, and an increased incidence and/or severity of mononuclear cell infiltrates at the injection sites in males and/or females administered ≥ 10 nmol/kg/dose. These findings persisted through the recovery phase in animals administered 100 nmol/kg/dose. However, the effects were considered non-adverse due to their mild severity and lack of impact on animal health and wellbeing. The no-observed-adverse-effect level (NOAEL) was 100 nmol/kg/dose. This dose level corresponded to maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from 0 to 24 hours postdose (AUC_{0-24}) values of 27.6 ng/mL and 174 ng·hr/mL, respectively, in males and 24.9 ng/mL and 128 ng·hr/mL, respectively, in females on Day 88 of the dosing phase.

In cynomolgus monkeys, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included mononuclear cell infiltrates at the SC injection sites of animals administered ≥ 10 nmol/kg/dose. This finding was not resolved with the completion of the recovery phase. However, the effects of 100 nmol/kg/dose were considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing. The NOAEL was 100 nmol/kg/dose (equivalent to 462.29 μg/kg/dose), which corresponded to C_{max} and AUC from 0 to 72 hours postdose (AUC_{0-72}) values of 121 ng/mL and 2840 ng·hr/mL in males, respectively, and 216 ng/mL and 4840 ng·hr/mL in females, respectively, on Day 88 of the dosing phase.

The genotoxic and mutagenic potential of OLP-1002 was evaluated with standard Good Laboratory Practice (GLP) via in vitro bacterial mutagenicity and chromosomal aberration studies, and was found to be negative.

1.5. Summary of Nonclinical Pharmacokinetics

In rats, following a single SC dose of ^{14}C-OLP-1002, the time of maximum observed concentration (T_{max}) was 0.5 to 1 hour for both radioactivity and parent compound. Plasma concentrations of total radioactivity were quantifiable through the last sampling time of 72 hours postdose, but was variable for the parent compound. The elimination half-life ($t_{1/2}$) of total radioactivity from plasma was 23 hours. Total radioactivity distributed into tissues, including those of the CNS protected by the blood-brain barrier. ^{14}C-OLP-1002-derived total radioactivity was not rapidly excreted from rats, with minimal amounts present in urine and feces. The bulk of the total radioactivity remained in carcasses, primarily in kidneys (cortex and medulla) and liver. Parent ^{14}C-OLP-1002 was present in plasma and tissues, but concentrations declined over time and were substantially lower than total radioactivity concentrations at the later sampling times.

After a single SC administration of ^{14}C-OLP-1002 to rats, the highest concentrations of total radioactivity were retained predominantly in the liver (10.4% to 13.3% of the dose), kidney cortex (3.47% to 4.96%), and kidney medulla (1.10% to 1.59% of the dose) through 168 hours postdose. For all other tissues, the total amounts of total radioactivity were substantially less, ranging from 0.0000203% in the 5th DRG to 0.327% in the spleen. Radioactivity was excreted slowly via both the renal and fecal routes of elimination. Total average recoveries of radioactivity in urine and feces through 336 hours postdose accounted for 2.31% and 1.75% of the administered radioactivity, respectively. The bulk of the administered total radioactivity was retained in the rat carcasses through 168, 336, 504, and 840 hours postdose. The kidney cortex, kidney medulla, and liver were the 3 tissues that retained the greatest amounts of the administered radioactivity.

Following a 16.1-µg/kg dose in rats, the plasma concentrations were still quantifiable at 72 hours postdose and the rate of elimination was slow, with $t_{1/2}$ 17.5 hours. It was not possible to accurately define the elimination phase for the 2.67- and 5.28-µg/kg dose levels.

In cynomolgus monkeys, following a single SC dose of ^{14}C-OLP-1002, T_{max} ranged from 0.25 to 1 hour for both total radioactivity and parent compound. Concentrations of total radioactivity were sustained in blood and plasma through the last sampling time of 144 hours postdose. Concentrations of parent compound were sustained in plasma through the last sampling time of 144 hours postdose in 2 of 3 monkeys, and were similar to plasma total radioactivity concentrations at 8 hours postdose. From 24 to 144 hours postdose, plasma concentrations of total radioactivity were substantially higher than for parent ^{14}C-OLP-1002 plasma concentrations.

The mean C_{max} of parent ^{14}C-OLP-1002 in plasma was 1.96 ng/mL. The mean plasma T_{max} was 0.833 hours. Plasma exposure of parent ^{14}C-OLP-1002 based on AUC extrapolated to infinity ($AUC_{0-\infty}$), was 12.7 ng·h/mL. After reaching C_{max}, plasma concentrations of parent ^{14}C-OLP-1002 declined with a mean $t_{1/2}$ of 84 hours.

1.6. Study Rationale

This is the first time OLP-1002 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data when OLP-1002 is administered SC as single and multiple doses to healthy subjects. This information, together with the pharmacodynamic (PD) and pharmacokinetic (PK) data, will help establish the doses and dosing regimen suitable for future studies in patients. The analgesic effects of OLP-1002 on a capsaicin-induced pain model will also be investigated.

1.7. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. For subjects in the PD assessment groups in Part A there will be some additional discomfort from the capsaicin test. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with OLP-1002 may be found in the Investigator's Brochure[4].

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is to assess the safety and tolerability of single and multiple SC doses of OLP-1002 in healthy subjects.

The exploratory objectives of the study are to evaluate the PD effect of OLP-1002 following single SC doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of single SC doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- incidence and severity of AEs
- vital signs measurements (blood pressure, pulse rate, respiratory rate)
- 12-lead electrocardiogram (ECG) parameters
- incidence of clinical laboratory abnormalities, based on clinical chemistry, hematology, and urinalysis test results
- physical examinations
- injection site assessment.

- demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.

2.2.2. Exploratory Endpoints

The following exploratory objectives will be assessed:

- pain intensity and duration will be assessed by AUC, maximum pain intensity (E_{max}), and time of maximum pain intensity (tE_{max}), calculated using a capsaicin-evoked pain model. The exploratory endpoint of secondary hyperalgesia will be assessed by the area of secondary area of hyperalgesia (Part A only).
- continuous (24-hour) ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval (Part A).
- heat pain threshold measurements and heat pain tolerance measurements.
- For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:

  Primary PK

  - area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])
  - AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)
  - maximum observed plasma concentration (C_{max}) (actual and DN)

  Secondary PK

  - time of the maximum observed plasma concentration (t_{max})
  - apparent plasma terminal elimination half-life ($t_{1/2}$)
- For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:

  Primary PK:

  - AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)
  - $AUC_{0-\infty}$ (actual and DN)
  - C_{max} (actual and DN)

  Secondary PK

  - minimum observed plasma concentration (C_{min})
  - t_{max}
  - $t_{1/2}$
  - observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)
  - observed accumulation ratio based on C_{max} (RAC_{max}).
  - Temporal change parameter (TCP)

Other PK parameters may also be added if deemed necessary.

3. INVESTIGATIONAL PLAN

This will be a double-blind, randomized, placebo-controlled, single and multiple SC dose study conducted in 2 parts.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, PK, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

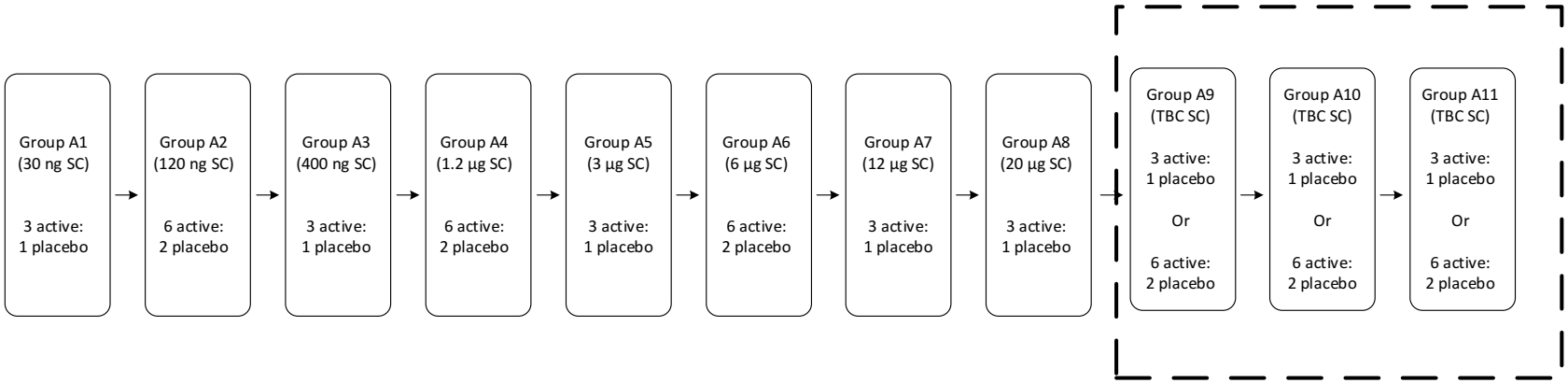
Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 10 (216 hours postdose) from the lower dose levels. For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.

In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, and A6 will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.

Sentinel dosing will be employed for all groups in Part A. To maintain the blind in a 4-subject group, the first subject will be dosed 48 hours before the second subject, and the second subject will be dosed 48 hours prior to the third and fourth subjects. In PD assessment groups, 2 subjects (1 active: 1 placebo) will be dosed 48 hours before the remaining 6 subjects (5 active: 1 placebo).

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic (Part A)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
Groups A9 to A11 may be included if required; dose levels will not exceed the maximum proposed dose of 20 µg.
Three groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

3.1.2. Part B

Part B will comprise a multiple-dose, sequential-group study. Overall, 24 subjects will be studied in 3 groups (Groups B1 to B3), with each group consisting of 8 subjects. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety and tolerability (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15.

All subjects will return for non-residential visits on Days 18 (± 2 days), 22 (± 2 days), 25 (± 2 days), and 29 (± 2 days), and for a poststudy visit on Day 57 (± 2 days).

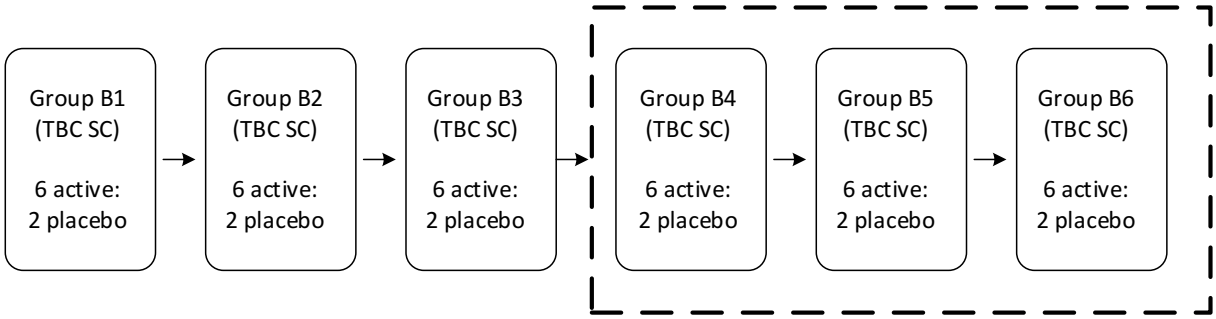
In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from the lower dose levels. Part B may start after a review of the safety, tolerability, and available PK for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

An overview of the study design is shown in Figure 2.

Figure 2: Study Schematic (Part B)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
All doses will be confirmed based on results of Part A; dose levels will not exceed the maximum proposed dose of 20 µg..
Groups B4 to B6 will be included if required.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 12 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Start of Study and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, PK, and PD data (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7]), additional dose groups may be added to the study. The maximum dose for any additional group will not exceed 20 µg. Up to 3 further groups of 8 subjects (6 active: 2 placebo) may be included in Part A, and up to 3 additional groups of 8 subjects (6 active: 2 placebo) may be included in Part B. The requirement for additional groups will be agreed with the Sponsor and documented in the Trial Master File (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential-group, ascending-dose design has been chosen for safety reasons as OLP-1002 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Subcutaneous doses have been chosen for both parts of the study, as this is the intended clinical route of administration.

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of

OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.

This study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Continuous ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing in Part A for groups consisting of 4 subjects will be such that there will be 48 hours between the first and second subjects, and 48 hours between the second and remaining 2 subjects in each group. For groups in Part A consisting of 8 subjects, 2 subjects (1 active: 1 placebo) will be dosed 48 hours prior to the remaining 6 subjects.

In Part B, sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.

In Parts A and B, there will be a minimum interval of a 10-minute gap between dosing subjects (when dosed on the same day). Continuation to dose the remaining subjects in a group will be at the Investigator's discretion.

3.4.2. Pharmacodynamic Assessment

Pharmacodynamic assessments will be conducted for subjects in Groups A2, A4, and A6.

Human experimental pain models using healthy volunteers can be used to assess the effect of a drug or treatment under controlled clinical conditions. Capsaicin is a vanilloid responsible for the pungent taste of hot peppers. In mammalian species, capsaicin-induced pain is mediated through Group C nerve fibers following activation of vanilloid 1 transient receptor potential (TRPV1) channels[5]. $Na_v1.7$ has been implicated in controlling neuropeptide release from C-fibers, and suppression of capsaicin-induced neurogenic flair has been demonstrated by an $NA_v1.7$ inhibitor[6].

Several studies have used intradermal capsaicin for human experimental pain studies[7,8]. It has been possible to demonstrate dose-dependent responses, with intradermal injections of 100 µg generally agreed to be the ideal dosage for these studies. Intradermal injection of capsaicin causes a brief stinging/burning pain at the injection site (spontaneous pain) followed by development of secondary hyperalgesia, which can be assessed using equipment such as Von Frey hairs. A study by Gazerani et al.[5] found that the response was site-specific and while peak pain intensity and duration were greatest in the forehead it was found that areas of visible flare and secondary hyperalgesia were significantly larger in the forearm, making the forearm the most suitable site for experimentation.

Covance CRU, Leeds, UK in 2009 performed a validation study using intradermal capsaicin (Covance CRU Study: 9999-004) with between-subject and within-subject variability demonstrating that the assessments can be reliably conducted to assess pharmacological response.

For these reasons, it has been decided to:

- Measure both capsaicin-evoked pain and secondary hyperalgesia.
- Limit the number of capsaicin tests to 3 for each subject (pre-screening, baseline, and 48 hours postdose)
- Exclude subjects who have pain <3 or >9 (using a Visual Analogic Scale [VAS]) at the pre-screening visit from PD assessment groups.

3.5. Selection of Doses in the Study

3.5.1. Starting Dose

The rat has been identified as the most sensitive species in a 13-week SC toxicity study with a 4-week recovery phase (Covance study no. 8355564). The NOAEL was the 100 nmol/kg/dose (462.29 µg/kg/dose). This dose level resulted in C_{max} of 27.6 ng/mL and 24.9 ng/mL in males and females, respectively, and AUC_{0-24} of 174 ng.h/mL and 128 ng.h/mL in males and females, respectively[4]. As the exposure was lower in the female rats these data have been used to calculate the safety margins.

The dose of 462.29 µg/kg/dose corresponds to human equivalent doses (HEDs) of 74.8 µg/kg/dose, which gives a maximum recommended starting dose (MRSD) of 444 µg for a 60-kg human and thus a 15000-fold safety margin to the proposed starting dose of 30 ng and 22-fold margin to the proposed maximum dose of 20 µg. Additionally the NOAEL dose in the cynomolgus monkey was identified as 100 nmol/kg/dose (462.29 µg/kg/dose), which gives a higher HED of 150 µg/kg/dose.

In vivo, doses of 10 pmol/kg/dose (0.0462µg/kg/dose) or less were found to inhibit peripheral acute inflammatory pain. The equivalent human dose for a 60-kg human is 44 ng, thus a dose at which minimal biological effect is anticipated has been selected as the starting dose of 30 ng.

3.5.2. Exposure

Human exposures have been estimated from the pharmacokinetics in the cynomolgus monkey since a non-human primate represents the most closely related species. Approximately dose-proportional exposure was seen in the 13-week toxicity study (Covance study no. 8355565) and ^{14}C pharmacokinetic study (Covance study no. 8355568) over a dose range of approximately 1.1 to 100 nmol/kg (5.06 to 462.29 µg/kg)[4]. However, the lowest dose (5.06 µg/kg) from the ^{14}C study has been used to estimate the human exposures as it is closest to the proposed human dose range and has the sufficient quantifiable data.

The assumptions made in the human exposure estimation were that human exposure would be similar to the cynomolgus monkey and that exposure would be linear with dose. Following a dose of 5.06 µg/kg in the cynomolgus monkey, the C_{max} was 1.96 ng/mL and $AUC_{0-\infty}$ was 12.7 ng.h/mL. The extrapolated exposures at the planned human doses are shown in Table 1 with margins calculated to the exposures at the NOAEL in the female rat.

Table 1: Estimated Human Exposure and Safety Margins to the NOAEL in the Female Rat for Single Dose Administration of OLP-1002

Human dose		Single dose to human		Safety margins for single dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\infty}$
0.03	0.000500	0.000194	0.00125	129000	102000
0.12	0.00200	0.000775	0.00502	32100	25500
0.4	0.00667	0.00258	0.0167	9640	7650
1.2	0.0200	0.0077	0.0502	3210	2550
3	0.0500	0.0194	0.125	1290	1020
6	0.100	0.0387	0.251	643	510
12	0.200	0.0775	0.502	321	255
20	0.333	0.129	0.837	193	153

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

The dosing interval currently anticipated for the multiple-ascending-dose part of this study is 72 hours or 96 hours. Thus the average dosing interval (82 hours) is similar to the half-life determined in the monkey ^{14}C study of 84 hours. Dosing at approximately once per half-life would be anticipated to result in accumulation of around 2-fold. However, higher levels of accumulation were observed (2.28-fold for C_{max} and 3.76-fold for AUC_{0-24}) on Day 88 at the top dose group (100 nmol/kg, 462.28 µg/kg) in the 13-week cynomologus monkey toxicity study following twice-weekly dosing (every 72 or 96 hours). Calculations were performed to estimate the likely human half-life using a standard 1-point allometric approach from the ^{14}C cynomolgus monkey pharmacokinetic study data. The exponents used were 0.75 for apparent total plasma clearance (CL/F) and 1 for apparent volume of distribution (V_z/F) values combined with the average body weight of the animal (3.1 kg) and scaling to a 60 kg human [9–11]. This resulted in a human half-life estimate of 180 h which in turn gave an accumulation estimate of 3.7-fold based upon a dosing interval of 82 h. This further supports the use of the greater than 2-fold accumulation from the 13-week cynomolgus study to estimate exposure following multiple dosing. Multiplication of the exposure estimates for the single ascending

dose by 2.28 for C_{max} and 3.76 for AUC resulted in exposure estimates for multiple dosing presented in Table 2.

Table 2: Estimated Human Exposure and Safety Margin to the NOAEL in the Female Rat for Multiple Dose Administration of OLP-1002

Human dose		Multiple dose to human		Safety margins for multiple dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\tau,ss}$
0.03	0.000500	0.000442	0.00472	56000	27000
0.12	0.00200	0.00177	0.0189	14100	6800
0.4	0.00667	0.00589	0.0629	4230	2030
1.2	0.0200	0.017663	0.189	1410	680
3	0.0500	0.0442	0.472	560	270
6	0.100	0.0883	0.944	282	136
12	0.200	0.177	1.89	141	68
20	0.333	0.294	3.15	85	41
30	0.500	0.442	4.72	56	27

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

3.5.3. Proposed Doses

The proposed IMP dose levels for Parts A and B are shown in Table 3.

Table 3: Proposed Investigational Medicinal Product Dose Levels for Parts A and B

Study Part	Group	Dose (OLP-1002)
Part A	A1	30 ng or placebo
	A2	120 ng or placebo
	A3	400 ng or placebo
	A4	1.2 µg or placebo
	A5	3 µg or placebo
	A6	6 µg or placebo
	A7	12 µg or placebo
	A8	20 µg or placebo
	A9*	TBC or placebo
	A10*	TBC or placebo
	A11*	TBC or placebo
Part B	B1	TBC or placebo
	B2	TBC or placebo
	B3	TBC or placebo
	B4*	TBC or placebo
	B5*	TBC or placebo
	B6*	TBC or placebo

Abbreviations: TBC = to be confirmed
* groups to be included if required.

In Parts A and B, there should not be an increase of > 3-fold between dose levels above 120 ng.

For Part B, dose levels, dosing frequency, and dosing duration will be decided, in consultation with the Sponsor, on the basis of data from Part A of the study. Since predictions of human exposure of OLP-1002 suggest that OLP-1002 concentrations may be not be quantifiable and human data have been estimated from a single species, it is proposed that the highest dose in the multiple-ascending-dose part will be up to 50% of the highest dose in the single-ascending-dose part (ie, if the highest dose in the single-ascending-dose part is 20 µg, the highest dose in the multiple-ascending-dose part will be 10 µg). Therefore, if the predicted accumulation of 3.7-fold occurs, the highest exposure in the multiple-ascending-dose part will not exceed ~2-fold the maximum exposure in the single-ascending-dose part.

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

3.6. Dose Escalation

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002. For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of 3 or 4 subjects, respectively, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

The justification for this is as follows:

- The study drug is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.

- A minimum of 3 subjects receiving the active drug is considered sufficient to characterize the safety profile for OLP-1002.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarizing results from all available safety assessments, will be sent to the Sponsor and a dose-escalation meeting will occur prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PD data may also be reviewed on an ongoing basis. In the event of a disagreement between Sponsor and Investigator on the dose-escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- One or more subjects experience an SAE that is considered to be related to OLP-1002.
- Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase (defined as 3 times the upper limit of normal), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least 1 occasion within a 24-hour interval in ≥1 subject in a group.
- The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).

If the sponsor deems it appropriate to resume dosing after the internal safety review, it can be done after the approval of a substantial protocol amendment.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Healthy male or females of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) between 18.0 and 28.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, single 12-lead ECG (resting heart rate > 45 bpm and < 90 bpm), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening as assessed by the Investigator (or designee).
4. Willing to abide by the contraception requirements as detailed in Appendix 4.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Any of the following:
    - QTcF > 450 ms confirmed by repeat measurement.
    - QRS duration > 110 ms confirmed by repeat measurement.
    - PR interval > 220 ms confirmed by repeat measurement.
    - findings which would make QTc measurements difficult or QTc data uninterpretable.
    - history of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
4. Female subjects who are pregnant or breastfeeding.
5. History of alcoholism or drug/chemical abuse within 1 year prior to Screening.

6. Alcohol consumption of > 21 units per week for males and >14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
7. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
8. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2).
9. Active skin conditions such as dermatitis, allergy, eczema, psoriasis, or abnormal healing.
10. Tattoos, scars, or moles that in the opinion of the Investigator are likely to interfere with dosing or study assessments at any of the potential injection sites.
11. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days or 5 half-lives of the investigational product, whichever is longer, prior to Check-in.
12. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
13. Use or intend to use any prescription medications/products other than hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptive concomitant medications within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
15. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and/or Sponsor have given their prior consent.
16. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in.
17. Receipt of blood products within 60 days prior to Check-in.
18. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
19. Poor peripheral venous access.
20. Have previously completed or withdrawn from this study or any other study investigating OLP-1002, and have previously received the investigational product.
21. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
22. Part A – PD assessment groups only
    - Subjects considered non-acceptable responders to the intradermal capsaicin test at screening, defined as maximum VAS score of < 3.0 or > 9.0.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number at the time of their randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A, Subjects 101, 102, etc., in Part B Subjects 201, 202, etc.). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal, including:
    - a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),
    - severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),
    - elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),
    - QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),
    - Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),
    - Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Vials of OLP-1002 Injection Solution 100 µg/mL (1.5 mL in 5-mL vials) and the Diluent for OLP-1002 Injection Solution (5 mL in 10-mL vials) will be supplied by the Sponsor, along with the batch/lot number and Certificate of Analysis. The Diluent for OLP-1002 Injection Solution will also be used as the Placebo formulation. A certificate of batch certification and release, authorized by a Qualified Person in the European Union (EU) will also be issued, by a Covance CRU Qualified Person, for each batch of IMP imported into the EU.

The IMPs will be stored according to the instructions on the label at the CRU in a location that is locked with restricted access.

Dose solutions (OLP-1002 Injection Solution diluted with the Diluent for OLP-1002 Injection Solution) will be prepared by Covance CRU Pharmacy staff in accordance with instructions provided in the Pharmacy Manual. The Placebo formulation will be the Diluent for OLP-1002 Injection Solution without further manipulation.

5.2. Study Treatment Administration

Subjects will be administered the IMP in numerical order. OLP-1002 will be administered by SC injection in the upper arm. If subcutaneous dosing of OLP-1002 in the upper arm is not possible, the subject may be dosed in the abdomen at the Investigator's discretion. For subjects in Groups A2, A4, and A6, dosing will be on the opposite arm to the intradermal capsaicin test.

5.3. Randomization

The randomization code will be produced by the statistics department at Covance using a computer-generated pseudo-random permutation procedure. In Part A, 1 subject in groups

consisting of 4 subjects, and 2 subjects in groups consisting of 8 subjects, will be randomly assigned to receive placebo. In Part B, 2 subjects per group will be randomly assigned to receive placebo. All other subjects in a group will be randomized to receive OLP-1002.

Prior to the start of the study, a copy of the master randomization code will be supplied into the Covance CRU pharmacy staff (in sealed envelopes).

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo solution will be identical in appearance to the OLP-1002.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

To maintain the blind, the Investigator will be provided with sealed randomization code-break envelopes for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose-escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

All doses of IMP will be administered by suitably qualified study site staff.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription medications/products from 14 days prior to dosing until the Follow-up visit, and non-prescription medications/products from 7 days prior to dosing until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests. On dosing days, subjects will receive a light breakfast approximately 2 hours prior to dosing. Meals will be provided as appropriate at other times and water will be freely available at all times.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until the Follow-up visit.

Xanthine-containing foods and beverages will not be allowed from 36 hours before Check-in until Discharge from the site. Xanthine-containing foods and beverages will also not be allowed form 36 hours before non-residential site visits.

Chili pepper/hot sauce will not be allowed for 48 hours prior to Check-in for all subjects. Subjects in Groups A2, A4, and A6 will not be allowed chili pepper/hot sauce for 48 hours prior to their pre-screening visit.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until Discharge. Following discharge, up to 2 units/day of alcohol are permitted until 36 hours before each non-residential visit and the Follow-up visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 3 days before Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during this

time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit. Subjects should not be in receipt of blood products for 60 days prior to check-in.

6.6. Other Restrictions

Subjects in Groups A2, A4, and A6 will not be allowed to shower within 1 hour prior to the capsaicin-evoked pain tests at prescreening, predose, and postdose.

Subjects will not be allowed to apply moisturizing creams or oils to the dosing site within 1 hour prior to dosing, or to the assessment site within 1 hour prior to the capsaicin-evoked pain test.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- vital signs
- blood samples
- cardiac monitoring/ECG extractions
- any other procedures.

7.1. Pharmacokinetic Assessments

7.1.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, PK analysis will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the

event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Pharmacodynamic Assessments

Capsaicin intradermal test will be performed for subjects in Groups A2, A4, and A6. Each subject will be tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).

7.2.1. Capsaicin-evoked Pain Model

The capsaicin model will be conducted by intradermal injection of capsaicin (100 µg in 100 µL of sterile saline containing 8% [w/w] Tween 80) into the skin of the anterior aspect of the forearm, midway between the elbow and the wrist. The bleb area (wheal) will be a sign of local plasma extravasation. An assessment of the pain intensity related to capsaicin injection will be estimated by repeated use of a VAS from injection to 5 minutes post-injection or until the pain intensity returned to zero. The AUC, E_{max}, and tE_{max} will be calculated and reported using dedicated software.

7.2.2. Secondary Hyperalgesia

The area of secondary hyperalgesia will be quantified with a 60-g weighted von Frey hair, by stimulating along 8 linear paths (4 vectors crossing at the location of the injection site) arranged vertically and horizontally around the stimulation site in 5-mm steps (starting approximately 6 cm away from the injection site). The area of secondary hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection.

7.3. Safety and Tolerability Assessments

Safety and tolerability assessments will be conducted at the times indicated in the Schedule of Assessments (Appendix 6). Timepoints may be adjusted based on an ongoing review of the data, and additional assessments may be conducted if deemed necessary by the Investigator or designee.

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked

about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a follicle-stimulating hormone (FSH) test and pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

Subjects must be supine for at least 5 minutes before blood pressure, pulse rate, and respiratory rate measurements.

7.3.4. Electrocardiogram

7.3.4.1. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value > 500 msec
- QTcF change from the mean baseline (Day 1 predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.4.2. Continuous (24-hour) Electrocardiogram

At the times indicated in the Schedule of Assessments (Appendix 6), continuous (24-hour) ECGs will be performed.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint. Each extraction will last for 5 minutes. Environmental distractions (eg, television, playing games, radio, conversation) should be avoided during the pre-ECG time window.

Continuous 24-hour ECGs are not planned for Part B of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.3.5. Heat Pain Threshold Test

Heat pain threshold tests will be conducted at the times indicated in the Schedule of Assessments (Appendix 6).

A computer-controlled thermal sensory analyzer device will be used to measure the heat pain threshold and tolerance level of the subjects. The heat pain assessments will be conducted on the subject's thigh.

Heat Pain Threshold:

For heat pain threshold measurements, the thermode will be placed directly on the skin of the right thigh, within an area selected before the start of the experiment and defined by surgical marking. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in

their dominant hand, to indicate when the heat pain threshold (first sensation of heat pain) is reached by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Heat Pain Tolerance:

For heat pain tolerance measurements, the thermode will be placed within the same surgically marked skin area of the anterior side of the right thigh, which was used to assess heat pain threshold. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in their dominant hand, to indicate when the heat-evoked pain has reached an intensity that is no longer tolerable, by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Safety Precautions

As there is a risk that OLP-1002 may affect the heat pain threshold, Covance CRU will put appropriate safety measures in place to ensure that subjects are not exposed to extremes of temperature when taking a shower or consuming hot drinks. During the heat pain safety assessments, the cut-off temperature for either test is 53 °C in order to prevent skin injury.

7.3.6. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

7.3.7. Body Weight and Height

Body weight (in underclothes) and height will be recorded at the times indicated in the Schedule of Assessments in Appendix 6. BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{body weight (kg)}}{(\text{height [m]})^2} \quad (\text{kg/m}^2)$$

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. In order to achieve PD endpoints in Part A, additional subjects will be included in 3 groups (8 subjects in total; 6 active: 2 placebo). Up to 3 additional groups may be added to Part A, consisting of either 4 subjects

(3 active; 1 placebo) or 8 subjects (6 active; 2 placebo). Up to 3 additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.2. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.3. Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

8.4. Pharmacodynamic Analyses

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned.

8.5. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- Mild: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but posing no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- Not Related: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- Unlikely Related: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- Related: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at the Follow-up visit will be followed up, where possible,

until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit (CRU). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Covance Drug Safety Services (DSS) Europe, Maidenhead, UK are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to DSS and the Sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Covance DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 2 working days of the initial notification to DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy reported by female subjects or

the female partners of male subjects should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total protein Urea	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[a]:	**Drug screen[b]:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test MDMA Alcohol breath test	Follicle-stimulating hormone[a] Serum pregnancy test (human chorionic gonadotropin)[a] Urine pregnancy test[c]

[a] Only analyzed at Screening.
[b] Only analyzed at Screening and Check-in.
[c] A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis*	4	19	
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			109.5

Part B

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	4	29	116
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			194.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject during the study will not exceed that donated during a standard blood donation (approximately 500 mL).

Appendix 4: Contraception Guidance

Definitions

Females of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Females of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary highly effective and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary highly effective methods of contraception include:

- surgical method performed at least 3 months prior to the Screening visit:
  - bilateral tubal ligation
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)
- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects can only choose a cervical cap or diaphragm if they have already had a prescription and fitting by their healthcare provider to ensure protocol requirements are met. Female subjects of childbearing potential should refrain from donation of ova from Check-in until 90 days after the Follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide
- vasectomised male subject (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success).

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the Follow-up visit.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the Follow-up visit.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a

public registry, all identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled and randomized subject, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

Study Plan – Part A (Single Dose)

	Pre-screening [d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Urine drugs of abuse screen		X	X							
Alcohol breath test		X	X							
Cotinine test		X	X							
Serology		X								
Hormone panel		X								
Urine pregnancy test[a]		X	X							X
Informed consent	X	X								
Study residency:										
Check-in			X							
Check-out					Day 3 (48 hours postdose)					
Non-residential visit	X	X				X	X	X	X	X
Study drug administration:					Day 1 (0 hours)					
Safety and tolerability:										
Adverse event recording		X	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording		X	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature		X			Predose, 1, 2, 4, 8, 24 (± 1 hour), and 48 hours postdose	X	X	X	X	X

	Pre-screening [d]	**Screening**	**Day -2**	**Day -1**	**Days 1 to 3**	**Day 4**	**Day 7 (± 2 days)**	**Day 10 (± 2 days)**	**Day 14 (± 2 days)**	**Poststudy (Day 28 ± 2 days)**
Supine 12-lead ECG		X			Predose, 4, 24 (± 1 hour) and 48 hours postdose		X		X	X
Continuous ECG extraction[b,c]				-24, -23.5, -23, -22.5, -22, -21.5, -21, -20, -18, -16, -12 hours	Day 1: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours					
Heat pain threshold test (heat pain threshold and heat pain tolerance)					Day 1: predose, 2, 4, 12, and 24 hours postdose (± 1 hour)					
Clinical chemistry, haematology, and urinalysis		X			48 hours postdose		X		X	X
Height and BMI		X								
Body weight		X	X							X
Physical examination		X								
Symptom-directed physical examination					Prior to discharge		X		X	X

	Pre-screening [d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Injection site assessment					Predose, 1, 2, 4, 8, 24, 48 hours postdose		X		X	X
Pharmacokinetics[e]										
Blood sampling					Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose	X	X	X	X	X
Pharmacodynamics[d]:										
Intradermal capsaicin test (capsaicin-evoked pain and secondary hyperalgesia measurement)	X		X		Day 2 (The area of secondary area of hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection)					

Abbreviations: BMI = body mass index; ECG = electrocardiogram.
[a] A positive urine pregnancy test result will be confirmed with a serum pregnancy test.
[b] All times are relative to dosing with OLP-1002.
[c] Continuous ECG recording may begin at approximately 25 hours before dosing to allow for checks to be completed prior to the first extraction timepoint and will continue for 24 hours postdose, ie, until after the last timepoint for ECG extraction (24 hours postdose). At timepoints for ECG extractions, subjects will be supinely resting for a total of 15 minutes (10-minute supine rest period, 5-minute extraction). Data will be archived for potential future analysis and will not be available for review during the study.
[d] Pharmacodynamic assessment groups only.
[e] PK analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data.

Study Plan – Part B (Multiple Dose)

	Screening	Day -1	Days 1-15	Day 18 (± 2 days)	Day 22 (± 2 days)	Day 25 (± 2 days)	Day 29 (± 2 days)	Poststudy (Day 57 ± 2 days)
Inclusion/exclusion criteria	X							
Demographic data	X							
Medical history	X							
Urine drugs of abuse screen	X	X						
Alcohol breath test	X	X						
Cotinine test	X	X						
Serology	X							
Hormone panel	X							
Urine pregnancy test[a]	X	X			X		X	X
Informed consent	X							
Study residency:								
Check-in		X						
Check-out			Day 15 (48 hours postdose)					
Non-residential visit	X			X	X	X	X	X
Study drug administration:			Days 1, 4, 7, 10, and 13					
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature	X		Day 1: predose, 1, 2, 4 and 8 hours postdose Day 2, Day 4 (postdose), Day 5, Day 7 (postdose), Day 9, Day 10 (postdose), Day 12, Day 13: predose, 1, 2, 4 and 8 hours postdose, and Day 15	X	X	X	X	X

	Screening	Day -1	Days 1-15	Day 18	Day 22	Day 25	Day 29	Poststudy (Day 57 ± 2 days)
Heat pain threshold test (heat pain threshold and heat pain tolerance)	X		Day 1 and Day 13: predose, 1, 2, 4, 8, 24 hours postdose					
Supine 12-lead ECG	X		Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Clinical chemistry, haematology, and urinalysis	X	X	Days 2, 4, 7, 10, 13		X		X	X
Height and BMI	X							
Body weight	X	X						X
Physical examination	X							
Symptom-directed physical examination			Days 1, 4, 7, 10, 13		X		X	X
Injection site assessment			Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Pharmacokinetics:								
Blood sampling[b]			Day 1 and Day 15: Pre dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post dose Days 4, 8, 11, 15 Predose	X	X	X	X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram.
[a] Positive urine pregnancy test results will be confirmed with a serum pregnancy test.
[b] PK timepoints will be reviewed based on emerging data and may be updated.

Appendix 7: Protocol Amendment Summary of Changes

Protocol Amendment 1 (Version 2; XX October 2018)

This amendment has been generated following the non-acceptance of the original protocol (version 1) by the Medicines and Healthcare products Regulatory Agency (MHRA) on 20 September 2018. All changes made have been in response to comments provided by the MHRA.

The primary changes in this amendment are:

1. Inclusion of PK sampling in Parts A and B:
    - PK objective and exploratory endpoints added (Section 2).
    - Discussion of PK included Section 3.4.
    - PK stopping criteria added to Section 3.7.
    - PK assessments included in Section 7.1.
    - PK population and analysis (Section 8.2.1).
    - Blood volumes updated to include samples for PK assessments (Appendix 3).
2. Exclusion and stopping criteria updated
    - Women who are pregnant or breastfeeding have been excluded from the study (Section 4.2).
    - Liver function tests, tachycardia, and hypertension stopping criteria have been updated (Section 3.7 and Section 4.4).
    - Stopping criteria for SAEs and serious AEs have been added (Section 3.7 and Section 4.4).
3. Safety, tolerability, and PK data up to Day 22 in Part B will be reviewed prior to dose escalation (Section 3.1.2).
4. Sentinel dosing included in Part B (Section 3.1.2).
5. It has been specified that the maximum dose for additional groups will not exceed 20 μg (Section 3.5.3).

Minor changes:

1. Additional clinical laboratory evaluations have been included on Day 14 in Part A.
2. The definition of the Safety population has been updated to include all subjects who receive OLP-1002.
3. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below. For each section, deleted text is shown in s~~trikethrough~~, and new text is shown in **bold**:

Section 1.6

Previously read:

This information, together with the pharmacodynamic (PD data, will help establish the doses and dosing regimen suitable for future studies in patients.

Now reads:

This information, together with the pharmacodynamic (PD) **and pharmacokinetic (PK)** data, will help establish the doses and dosing regimen suitable for future studies in patients.

Section 2.1

Objective added:

Where possible, single and/or multiple subcutaneous dose pharmacokinetics of OLP-1002 in healthy subjects will be determined.

Section 2.2.1

Endpoint added:

- **demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.**

Section 2.2.2

Endpoints added:

- **For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])**
  - **AUC from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)**
  - **maximum observed plasma concentration (C_{max}) (actual and DN)**

  Secondary PK

  - **time of the maximum observed plasma concentration (t_{max})**
  - **apparent plasma terminal elimination half-life ($t_{1/2}$)**

- **For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:**

  Primary PK

  - **AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)**
  - **$AUC_{0-\infty}$ (actual and DN)**
  - **C_{max} (actual and DN)**

  Secondary PK

  - **minimum observed plasma concentration (C_{min})**
  - **t_{max}**
  - **$t_{1/2}$**
  - **observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)**
  - **observed accumulation ratio based on C_{max} (RAC_{max}).**
  - **Temporal change parameter (TCP)**

Other PK parameters may also be added if deemed necessary.

Section 3.1.1

Previously read:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day ~~7~~ (~~144~~ hours postdose) from the lower dose levels.

Now reads:

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, **PK,** and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day **10** (**216** hours postdose) from the lower dose levels. **For doses ≥ 12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.**

Figure 1 – footnote

Text added:

Groups A9 to A11 may be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Figure 2 – footnote

Text added:

Groups B4 to B6 will be included if required**; dose levels will not exceed the maximum proposed dose of 20 µg**.

Section 3.1.2

Previously read:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. ~~There will be no sentinel dosing in Part B.~~ For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. The dosing

frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from the lower dose levels. Part B may start after a review of the safety ~~and~~ tolerability for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Now reads:

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from the lower dose levels. Part B may start after a review of the safety**,** tolerability**, and available PK data** for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

Section 3.3

Previously read:

Following review of the safety, tolerability, and PD data, additional dose groups may be added to the study.

Now reads:

Following review of the safety, tolerability, **PK,** and PD data **(where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria [Section 3.7])**, additional dose groups may be added to the study. **The maximum dose for any additional group will not exceed 20 µg.**

Section 3.4

Previously read:

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

~~Pharmacokinetic analysis will not be conducted in this study. T~~he bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose~~s~~ would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. ~~Thus, the additional burden of sampling procedures would not be justified by the quality of the data which it would generate.~~

Now reads:

In Part A, safety data up to Day 10 will be reviewed prior to dose escalation, and PK data up to Day 7 will be reviewed for all groups receiving ≥ 12 µg OLP-1002. In Part B, safety, tolerability and PK data up to Day 22 will be reviewed for all dose groups. As the $t_{1/2}$ of OLP-1002 is predicted to be approximately 180 hours (based on non-clinical data) review of safety data up to Day 10 (Part A) and Day 22 (Part B) is considered sufficient to ensure data from at least one half-life is included in the review. In addition, as plasma exposures are anticipated to be low, it is expected that it will only be possible to perform an assessment of peak concentrations (C_{max}) and therefore PK data to Day 7 (Part A) and Day 22 (Part B) will be sufficient. Additionally, a

cumulative safety review will occur such that additional emerging safety data from earlier groups will be considered when making a dose escalation decision.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis in Part A will initially only be conducted for groups receiving ≥ 12 µg OLP-1002, with retrospective analyses of samples from lower dose groups occurring in the event of PK data being quantifiable at doses ≥ 12 µg and if supported by bioanalytical stability data. Dose escalation decisions for doses <12 µg in Part A will not require PK data. The rationale for this is that maximum plasma concentrations at 12 µg are expected to be approximately 0.078 ng/mL and the bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. **Therefore, even with the increased assay sensitivity plasma levels from doses at or below 12 µg are not expected to be quantifiable.** It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest dose would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. **In addition the planned dose levels have a high safety margin when comparing the predicted exposures to the exposures at the NOAEL (see Section 3.5.2), with the 12 µg dose level having an expected 312-fold and 255-fold safety margin based on C_{max} and $AUC_{0-\infty}$, respectively. Therefore if exposure is significantly higher than predicted it is not expected to exceed the PK stopping criteria.**

Section 3.4.1

Previously read:

In Part B, ~~all subjects in a group will be dosed on the same day~~. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3).

Now reads:

In Part B, **sentinel dosing will be used in groups where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well tolerated in earlier groups in Parts A or B. When used, two subjects (1 active; 1 placebo), will be dosed 4 days prior to the remaining 6 subjects (5 active; 2 placebo). The 2 sentinel subjects will always be 2 doses ahead of the remaining subjects (ie. sentinel subjects will receive dose 2 before the remaining subjects receive dose 1). Subjects in groups where exposure is not predicted to exceed that tested in Part A will be dosed on the same day**. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3). **If it is not possible to quantify exposure it will be assumed that multiple dosing results in a 4-fold accumulation based on the predicted $t_{1/2}$ of 180h.**

Section 3.5.3

Text added:

If additional groups (A9-11 or B3-6) are required, the maximum daily dose administered will not exceed 20 µg and predicted systemic exposure will not exceed that stated in the dose escalation stopping criteria [Section 3.7]) based on available PK data.

Section 3.6

Previously read:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety ~~and~~ tolerability data up to Day ~~18~~ (~~120~~ hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of ~~5~~ subjects, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group,

such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Now reads:

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002. **For escalation to doses > 12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.**

In Part B, doses will be administered in an escalating manner following satisfactory review of safety**,** tolerability**, and PK** data up to Day **22** (**216** hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. **Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.**

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of **3 or 4** subjects**, respectively**, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

Section 3.7

Previously read:

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in ~~liver function tests (~~aspartate aminotransferase, alanine aminotransferase~~,~~ alkaline phosphatase ~~and total bilirubin)~~ defined as 3 times the upper limit of normal in ~~3~~ or more subjects in a group ~~(~~confirmed with repeat testing~~)~~.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.

- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least ~~2~~ occasion~~s~~ within a 24-hour interval in ~~at least 2~~ subject~~s~~ in a group.

Now reads:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- **One or more subjects experience an SAE that is considered to be related to OLP-1002.**
- **Two or more subjects in the same group experience severe non-serious AEs (ie. severe non-serious AEs considered as, at least, possibly related to OLP-1002 administration), independent of whether the AEs are within or not within the same system organ class.**
- There is evidence of clinically significant increases in aspartate aminotransferase, alanine aminotransferase **or** alkaline phosphatase **(**defined as 3 times the upper limit of normal**), or total bilirubin (defined as 2 times the upper limit of normal) that are considered to be related to OLP-1002 in 2 or more subjects in a group. Results will be** confirmed with repeat testing.
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least **1** occasion within a 24-hour interval in ≥**1** subject in a group.
- **The dose will not exceed 20 µg or the systemic exposure for any individual subject is predicted to exceed a C_{max} of 24.9 ng/mL (plasma) and/or an AUC_{0-24} of 128 ng/mL; i.e., systemic exposure will be no greater than the NOAEL in the most sensitive species (100,000 pmol/kg in rat [462 µg/kg]).**

Section 4.2

Exclusion criteria added:

4. Female subjects who are pregnant or breastfeeding.

Section 4.4

Previously read:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal

Now reads:

- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal**, including:**
  - **a serious adverse reaction (i.e., a SAE considered at least possibly related to OLP-1002 administration),**
  - **severe non-serious adverse reaction (i.e., severe non-serious AE considered to at least possibly related to OLP-1002 administration),**
  - **elevated AST, ALT, ALK (3 x ULN) or total bilirubin (2 x ULN),**
  - **QTcF increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement),**
  - **Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements),**
  - **Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements).**

Section 7.1

Section added:

7.1 Pharmacokinetic Assessments

7.1.1 Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Appendix 6). Furthermore, additional blood samples may be taken from each subject per treatment period, with the maximum volume of blood withdrawn per subject not exceeding the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from subjects who received placebo will not be analyzed.

In Part A, only samples collected from subjects that received >12 µg OLP-1002 will be initially analyzed. If PK data is quantifiable at concentrations of OLP-

1002 >12 µg, samples from lower dose groups will be retrospectively analyzed. In Part B, PK samples will be analyzed for all groups.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2 Analytical Methodology

Plasma concentrations of OLP-1002 will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

Section 8.2

Previously read:

8.2.~~1~~ Pharmacodynamic population

The PD population will include all subjects who received at least 1 dose of ~~study treatment~~ OLP-1002 or placebo and for whom PD can be evaluated.

8.2.~~2~~ Safety Population
The safety population will include all subjects who received at least 1 dose of ~~study treatment~~ or placebo ~~and have at least 1 postdose safety assessment~~.

Now reads:

8.2.1 Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of OLP-1002 that have evaluable PK data and have had no AEs or protocol deviations considered to impact PK.

8.2.**2** Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of OLP-1002 or placebo and for whom PD can be evaluated.

8.2.**3** Safety Population

The safety population will include all subjects who received at least 1 dose of OLP-1002 or placebo.

8.3 Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma and urine concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations of OLP-1002 and PK parameters will be listed and summarized using descriptive statistics. Individual and arithmetic mean OLP-1002 concentration-time profiles will also be presented graphically.

Appendix 3

Table updated:

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis*	**4**	**19**	**76**
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			~~33.5~~**109.5**

Part B

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Pharmacokinetic analysis	**4**	**29**	**116**
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			~~78.5~~**194.5**

Appendix 6

PK and Blood sampling rows added to the schedule of events for Part A and Part B. In the Schedule of events for Part A, footnote e was added. In the Schedule of events for Part B, footnote b was added.

Clinical chemistry, hematology, and urinalysis was added to the Schedule of events for Part A on Day 14.

Protocol

OLP-1002 – A First-in-human, Double-blind, Placebo-controlled, Single and Multiple Subcutaneous Dose, Safety, Tolerability, and Pharmacodynamic Study in Healthy Male and Female Subjects

Protocol Status: Final
Protocol Date: 31 August 2018
Protocol Version: 1

Investigational Product: OLP-1002

Protocol Reference Number: OLP-1002-001
Covance Study Number: 8379789
EudraCT Number: 2018-003085-13

Sponsor:
OliPass Corporation
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Study Site:
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United Kingdom

Sponsor Signatory:
[redacted]

Principal Investigator:
[redacted]

SPONSOR APPROVAL

I have read the protocol and approve it:

[redacted]

August 31, 2018

Date

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

[redacted]

[redacted]
Principal Investigator

31 August 2018
Date

STUDY IDENTIFICATION

Sponsor	OliPass Corporation Ace Dongbaek Tower 20th Floor 16 Beon-gil, 16-4 Dongbaek Jungang-ro Giheung, Yongin, Gyeonggi 17015 Republic of Korea
Sponsor's Study Contact	[redacted] OliPass Corporation Ace Dongbaek Tower 20th Floor 16 Beon-gil, 16-4 Dongbaek Jungang-ro Giheung, Yongin, Gyeonggi 17015 Republic of Korea
Sponsor's Medical Contact	[redacted] OliPass Corporation Ace Dongbaek Tower 20th Floor 16 Beon-gil, 16-4 Dongbaek Jungang-ro Giheung, Yongin, Gyeonggi 17015 Republic of Korea
Medical Monitor (24-hour emergency medical contact)	[redacted]
Study Site	Covance Clinical Research Unit Ltd. Springfield House, Hyde Street, Leeds, LS2 9LH United Kingdom
Principal Investigator	[redacted] Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH United Kingdom [redacted]
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	[redacted]
Clinical Laboratory	[redacted]
Statistician	[redacted] Covance

SYNOPSIS

Title of study: OLP-1002 – A first-in-human, double-blind, placebo-controlled, single and multiple subcutaneous dose, safety, tolerability, and pharmacodynamic study in healthy male and female subjects
Objectives: The primary objective of the study is to assess the safety and tolerability of single and multiple subcutaneous doses of OLP-1002 in healthy subjects. The exploratory objectives of the study are to evaluate the pharmacodynamic effect of OLP-1002 following single subcutaneous doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of a single subcutaneous doses of OLP-1002 on cardiac QT interval.
Study design: This will be a double-blind, randomized, placebo-controlled, single and multiple subcutaneous dose study conducted in 2 parts, including healthy male and female subjects.
Number of subjects: Part A: 44 subjects will be studied in 8 groups (5 groups of 4 and 3 groups of 8). Part B: 24 subjects will be studied in 3 groups (Groups B1 to B3). Up to 24 additional subjects may be recruited into Part A and Part B of the study if required.
Diagnosis and main criteria for inclusion: Healthy male and female subjects aged between 18 and 60 years (inclusive) with a body mass index between 18.0 and 28.0 kg/m^2 (inclusive).
Investigational products, dose, and mode of administration: Test product: OLP-1002 Proposed dose levels for Part A: 30 ng, 120 ng, 400 ng, 1.2 µg, 3 µg, 6 µg, 12 µg, and 20 µg. Proposed dose levels for Part B: the doses for Part B will be decided in consultation with the Sponsor and on the basis of data from Part A of the study. The highest dose in Part B will be up to 50% of the highest dose in Part A. Administration route: subcutaneous
Reference product and mode of administration: Reference product: placebo Administration route: subcutaneous
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to Follow-up): approximately 8 weeks for Part A and approximately 12 weeks for Part B.
Endpoints: **Pharmacodynamics:** In Part A, the analgesic effect of OLP-1002 will be investigated in 3 groups consisting of 8 subjects (6 active: 2 placebo) using experimental capsaicin-evoked pain methods. Measurement of capsaicin-evoked pain will be performed at pre-screening, baseline and on Day 2, and secondary hyperalgesia at 5 and 30 minutes post-capsaicin injection. Continuous electrocardiogram (ECG) recording will be conducted to investigate the effect of OLP-1002 on cardiac function. **Safety:** Adverse events, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis), 12-lead ECGs, vital signs measurements, injection site assessment, and physical examinations.

Statistical methods:
Pharmacodynamics:
Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of pharmacodynamic data is planned.
Safety:
Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours postdose
BMI	body mass index
C_{max}	maximum observed plasma concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSA	clinical study agreement
DRG	dorsal root ganglion
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
E_{max}	maximum pain intensity
FCA	Freund's Complete Adjuvant
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SC	subcutaneous(ly)
SNL	spinal nerve ligation
$t_{1/2}$	elimination half-life
tE_{max}	time of maximum pain intensity
T_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
VAS	Visual Analogic Scale
VGSC	voltage-gated sodium channel

1. INTRODUCTION

1.1. Overview

OLP-1002 is a novel peptide nucleic acid (PNA) derivative which acts as a specific voltage-gated sodium channel (VGSC) protein ($Na_v1.7$) inhibitor, and is being developed by OliPass for the treatment of pain.

The $Na_v1.7$ protein is a subtype of VGSCs. $Na_v1.7$ is particularly important in nociception and pain signaling, with congenital loss-of-function mutations in $Na_v1.7$ resulting in the inability to experience pain. Selective $Na_v1.7$ inhibitors are believed to have the potential to treat severe pain safely[1]. The active sites of VGSC subtypes are virtually indistinguishable by their 3-dimensional structure and thus the discovery of selective $Na_v1.7$ small molecule inhibitors has been extremely challenging. Since inhibition of $Na_v1.5$ subtype elicits long QT cardiotoxicity, inhibition of $Na_v1.5$ subtype should be avoided at therapeutic doses.

To date, there are several $Na_v1.7$ inhibitors claimed to be selective that have been evaluated in human subjects:

- Vixotrigine (formerly known as raxatrigine) inhibits $Na_v1.7$ as well as other VGSC subtypes. Vixotrigine is in phase III clinical development for trigeminal neuralgia. Due to the limited $Na_v1.7$ selectivity over $Na_v1.5$, vixotrigine was evaluated primarily in patients with a low heart risk.
- Funapide is a $Na_v1.7$ inhibitor with limited $Na_v1.7$ selectivity, and was in phase IIb clinical trials as of July 2014. Although funapide showed analgesic activity in a small number of erythromelalgia patients, dose-limiting adverse events (AEs), including dizziness and somnolence, were observed[2]. The central nervous system (CNS) AEs were due to its poor $Na_v1.7$ selectivity.
- PF-05089771 is a $Na_v1.7$ selective inhibitor with a claimed $Na_v1.7$ selectivity of > 2000-fold versus other subtypes of sodium channel and was evaluated in patients of erythromelalgia or dental pain. It is thought low drug concentrations achieved in the target tissue could be a possible explanation for its poor analgesic activity in human patients[3].

OLP-1002 is fully complementary to a 14-mer RNA sequence spanning the junction of intron 4 and exon 5 in the human SCN9A pre-mRNA which codes for the $Na_v1.7$ channel. OLP-1002 yields SCN9A mRNA splice variant(s) encoding variant $Na_v1.7$ protein(s) lacking the sodium channel activity (ie, a non-functional channel), thereby inhibiting $Na_v1.7$ channel function.

1.2. Summary of Nonclinical Pharmacology

1.2.1. In Vitro Pharmacology Studies

Overall, results from the in vitro pharmacology studies showed OLP-1002 elicits responses consistent with its designed function[4]. It inhibits SCN9A mRNA expression and yields the

$Na_v1.7$ variant protein or proteins lacking sodium channel activity. Its effects are highly selective, which may provide for an improved margin of safety compared to other $Na_v1.7$ inhibitors.

OLP-1002 at 1 to 100 zM in PC3 prostate carcinoma cells induced exon skipping and yielded SCN9A mRNA splice variant(s) encoding a $Na_v1.7$ variant protein or proteins lacking sodium channel activity.

In rat dorsal root ganglion (DRG) neuronal cells, OLP-1002 at 1000 zM inhibited $Na_v1.7$ protein expression by > 50%, while OLP-1002R at 100 and 1000 zM inhibited $Na_v1.7$ expression almost completely. As OLP-1002R is fully complementary to rat SCN9A pre-mRNA, OLP-1002R would be predicted to be more potent than OLP-1002 in this cell type.

SCN9A mRNA expression level was evaluated by quantitative polymerase chain reaction (qPCR). OLP-1002 inhibited the expression of the SCN9A mRNA in PC3 cells with sub-attomolar potency.

In SH-SY5Y human neuroblastoma cells stimulated with tumor necrosis factor (TNF)-1α to upregulate the expression of SCN9A mRNA, OLP-1002 decreased expression by 46% to 49% at 1 fM to 10 pM. In rat DRG neuronal cells, OLP-1002 at 1 fM significantly decreased SCN9A mRNA expression by 54%.

In rat DRG neuronal cells, OLP-1002 markedly and significantly inhibited the sodium current by 77% at 0.1 aM and 73% at 1 aM, while for OLP-1002R, the inhibition was 66% at 0.1 aM and 70% at 1 aM. Given that rat DRG neuronal cells express various subtypes of sodium channel, the observed inhibitions of 66% to 77% correspond to the complete knockout of the $Na_v1.7$ sodium channel subtype with OLP-1002 or OLP-1002R.

The $Na_v1.7$ selectivity over $Na_v1.5$ was evaluated in H9C2 rat cardiomyocytes which are known to abundantly express the rat $Na_v1.5$ sodium channel subtype. Following incubation with OLP-1002 or OLP-1002R at 1 aM or 1 pM, there were no notable decreases in the sodium current. Considering that OLP-1002 and OLP-1002R inhibit the expression of $Na_v1.7$ protein at 1 aM or lower in rat DRG neuronal cells, the $Na_v1.7$ selectivity of OLP-1002 and OLP-1002R over $Na_v1.5$ is estimated to be in excess of one million-fold. Such a large $Na_v1.7$ selectivity over $Na_v1.5$ has not been realized with small molecule $Na_v1.7$ inhibitors, suggesting that OLP-1002 potentially offers pain management with much greater cardiovascular safety.

1.2.2. In Vivo Pharmacology Studies

Spinal nerve ligation (SNL) has been widely applied as a rat model for neuropathic pain. OLP-1002 and OLP-1002R were found to be very potent, but highly variable in potency, in reversing neuropathic allodynia in this model. Analyses of the therapeutic potency strongly suggested that a marked proportion of subcutaneously (SC) administered OLP-1002 or OLP-1002R may have been topically delivered directly to the spinal nerves exposed in the dorsal cavity created during the SNL modelling. In addition, the variability of the therapeutic potency may be due to a variable degree of healing of the SNL surgery wound. If an animal

recovers slowly, the animal tends to be left with a dorsal cavity. Therefore, estimations of potency in these studies with this model should be treated with caution.

In one study using the SNL model, allodynia in rats was slowly and gradually reversed by OLP-1002 SC administered at nominal doses of 1, 3, and 6 pmol/kg once every 2 days (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). As the onset time for pain reduction was 4 days, the doses used were not sufficient for fast onset of activity. In this study, the animals should have reasonably recovered from the dorsal wound, and therefore less susceptible to topical delivery directly to the exposed spinal nerves. However, in another study in this model, when OLP-1002 was intraperitoneally (IP) administered once every 3 days to avoid the likelihood of local delivery to the spinal nerves, OLP-1002 surprisingly reversed the allodynia at 5 fmol/kg, and was superior or comparable to pregabalin 30 mg/kg, a gold standard for neuropathic pain studies. The high potency shown at 5 fmol/kg IP strongly suggests the possibility that OLP-1002 is efficiently absorbed by the enteric nervous system, travels to the spinal cord, and then redistributes to the spinal nerves of the SNL ligation. This opens the possibility of efficient oral delivery of OLP-1002 to the spinal cord.

When evaluated for their ability to reverse the inflammatory pain in rats inflicted with Freund's Complete Adjuvant (FCA)-induced severe paw inflammation, OLP-1002 at 300 pmol/kg and OLP-1002R at 100 pmol/kg significantly reversed the thermal hyperalgesia, and both were more effective than pregabalin 30 mg/kg.

Paw burn injury induces hyperalgesia in rats and is known to upregulate $Na_v1.7$ expression in the L5 and L6 DRGs of the affected side. Burn injury induces a far weaker degree of paw inflammation than FCA-induced paw inflammation. OLP-1002 SC administered inhibited the thermal hyperalgesia in paw burn injury in a dose-dependent manner. At 25 fmol/kg, OLP-1002 did not inhibit thermal hyperalgesia. Although OLP-1002 at 625 fmol/kg significantly inhibited the thermal hyperalgesia, the efficacy was moderate and weaker than pregabalin 30 mg/kg. This suggests that SC dosing does not offer the local topical delivery to spinal nerves in this model as seen in rats without a dorsal cavity wound. In this study, the $Na_v1.7$ expression in the DRG of the burn injury side significantly decreased by 58% with 625 fmol/kg OLP-1002, validating the target engagement for analgesic activity.

An intraplantar injection of formalin induces severe acute pain. The contributors to acute pain are known to be complex and require further elucidation. However, acute peripheral inflammation is known to contribute much to Phase II Pain (pain from 10 to 40 min after the formalin injection). In this model, OLP-1002 significantly inhibited Phase II Pain at comparable or saturated efficacy when SC administered at 10 to 100 pmol/kg (due to adhesion to the dosing equipment, the actual doses administered were estimated to be approximately 10% of the nominal values). Thus peripheral acute inflammatory pain could be treated with 10 pmol/kg or less.

1.2.3. Ex Vivo Pharmacology Studies

One day post-SC injection, OLP-1002 and OLP-1002R at 100 pmol/kg significantly inhibited the expression of $Na_v1.7$ protein by 39% and 57%, respectively, in the spinal cord of rats subjected to SNL.

In other rats subjected to SNL, OLP-1002R slowly and gradually reversed the allodynia in a dose-dependent manner. OLP-1002R at 30 fmol/kg (the highest dose administered) had the greatest effect, but the dose was not high enough to elicit full therapeutic efficacy. OLP-1002R inhibited expression of $Na_v1.7$ protein in these animals, most notably at 1 fmol/kg, and decreased SCN9A mRNA expression by approximately 40% at 1 to 30 fmol/kg. The observed inhibitions were largely consistent with the in vivo therapeutic activity findings.

Taking all the in vivo and ex vivo findings together, OLP-1002R was concluded to inhibit neuropathic allodynia by inhibiting the expression of the SCN9A mRNA and the $Na_v1.7$ protein.

1.3. Summary of Safety Pharmacology

In vitro, OLP-1002 did not inhibit the human ether-à-go-go-related gene (hERG) channel current expressed in human embryonic kidney (HEK) cells at the highest concentration tested 2 μM (the limit of the validated analytical method for OLP-1002).

In the in vivo safety pharmacology studies, OLP-1002 SC administered at dose levels up to 100 nmol/kg had no effect on body temperature, neurological function, or respiratory function in rats, and had no significant toxic effect on cardiovascular function in cynomolgus monkeys.

1.4. Summary of Toxicology

In rats, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included pigment accumulation in the kidney of males administered 100 nmol/kg/dose and females administered ≥ 10 nmol/kg/dose, foreign material and vacuolated macrophage infiltrates in males and/or females administered ≥ 1 nmol/kg/dose, and an increased incidence and/or severity of mononuclear cell infiltrates at the injection sites in males and/or females administered ≥ 10 nmol/kg/dose. These findings persisted through the recovery phase in animals administered 100 nmol/kg/dose. However, the effects were considered non-adverse due to their mild severity and lack of impact on animal health and wellbeing. The no-observed-adverse-effect level (NOAEL) was 100 nmol/kg/dose. This dose level corresponded to maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from 0 to 24 hours postdose (AUC_{0-24}) values of 27.6 ng/mL and 174 ng·hr/mL, respectively, in males and 24.9 ng/mL and 128 ng·hr/mL, respectively, in females on Day 88 of the dosing phase.

In cynomolgus monkeys, following twice-weekly SC dosing for 13 weeks, OLP-1002-related microscopic findings included mononuclear cell infiltrates at the SC injection sites of animals administered ≥ 10 nmol/kg/dose. This finding was not resolved with the completion of the recovery phase. However, the effects of 100 nmol/kg/dose were considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing. The NOAEL was 100 nmol/kg/dose (equivalent to 462.29 μg/kg/dose), which corresponded to C_{max} and AUC from 0 to 72 hours postdose (AUC_{0-72}) values of 121 ng/mL and 2840 ng·hr/mL in males, respectively, and 216 ng/mL and 4840 ng·hr/mL in females, respectively, on Day 88 of the dosing phase.

The genotoxic and mutagenic potential of OLP-1002 was evaluated with standard Good Laboratory Practice (GLP) via in vitro bacterial mutagenicity and chromosomal aberration studies, and was found to be negative.

1.5. Summary of Nonclinical Pharmacokinetics

In rats, following a single SC dose of ^{14}C-OLP-1002, the time of maximum observed concentration (T_{max}) was 0.5 to 1 hour for both radioactivity and parent compound. Plasma concentrations of total radioactivity were quantifiable through the last sampling time of 72 hours postdose, but was variable for the parent compound. The elimination half-life ($t_{1/2}$) of total radioactivity from plasma was 23 hours. Total radioactivity distributed into tissues, including those of the CNS protected by the blood-brain barrier. ^{14}C-OLP-1002-derived total radioactivity was not rapidly excreted from rats, with minimal amounts present in urine and feces. The bulk of the total radioactivity remained in carcasses, primarily in kidneys (cortex and medulla) and liver. Parent ^{14}C-OLP-1002 was present in plasma and tissues, but concentrations declined over time and were substantially lower than total radioactivity concentrations at the later sampling times.

After a single SC administration of ^{14}C-OLP-1002 to rats, the highest concentrations of total radioactivity were retained predominantly in the liver (10.4% to 13.3% of the dose), kidney cortex (3.47% to 4.96%), and kidney medulla (1.10% to 1.59% of the dose) through 168 hours postdose. For all other tissues, the total amounts of total radioactivity were substantially less, ranging from 0.0000203% in the 5th DRG to 0.327% in the spleen. Radioactivity was excreted slowly via both the renal and fecal routes of elimination. Total average recoveries of radioactivity in urine and feces through 336 hours postdose accounted for 2.31% and 1.75% of the administered radioactivity, respectively. The bulk of the administered total radioactivity was retained in the rat carcasses through 168, 336, 504, and 840 hours postdose. The kidney cortex, kidney medulla, and liver were the 3 tissues that retained the greatest amounts of the administered radioactivity.

Following a 16.1-µg/kg dose in rats, the plasma concentrations were still quantifiable at 72 hours postdose and the rate of elimination was slow, with $t_{1/2}$ 17.5 hours. It was not possible to accurately define the elimination phase for the 2.67- and 5.28-µg/kg dose levels.

In cynomolgus monkeys, following a single SC dose of ^{14}C-OLP-1002, T_{max} ranged from 0.25 to 1 hour for both total radioactivity and parent compound. Concentrations of total radioactivity were sustained in blood and plasma through the last sampling time of 144 hours postdose. Concentrations of parent compound were sustained in plasma through the last sampling time of 144 hours postdose in 2 of 3 monkeys, and were similar to plasma total radioactivity concentrations at 8 hours postdose. From 24 to 144 hours postdose, plasma concentrations of total radioactivity were substantially higher than for parent ^{14}C-OLP-1002 plasma concentrations.

The mean C_{max} of parent ^{14}C-OLP-1002 in plasma was 1.96 ng/mL. The mean plasma T_{max} was 0.833 hours. Plasma exposure of parent ^{14}C-OLP-1002 based on AUC extrapolated to infinity ($AUC_{0-\infty}$), was 12.7 ng·h/mL. After reaching C_{max}, plasma concentrations of parent ^{14}C-OLP-1002 declined with a mean $t_{1/2}$ of 84 hours.

1.6. Study Rationale

This is the first time OLP-1002 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data when OLP-1002 is administered SC as single and multiple doses to healthy subjects. This information, together with the pharmacodynamic (PD) data, will help establish the doses and dosing regimen suitable for future studies in patients. The analgesic effects of OLP-1002 on a capsaicin-induced pain model will also be investigated.

1.7. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. For subjects in the PD assessment groups in Part A there will be some additional discomfort from the capsaicin test. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with OLP-1002 may be found in the Investigator's Brochure[4].

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is to assess the safety and tolerability of single and multiple SC doses of OLP-1002 in healthy subjects.

The exploratory objectives of the study are to evaluate the PD effect of OLP-1002 following single SC doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of single SC doses of OLP-1002 on cardiac QT interval.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- incidence and severity of AEs
- vital signs measurements (blood pressure, pulse rate, respiratory rate)
- 12-lead electrocardiogram (ECG) parameters
- incidence of clinical laboratory abnormalities, based on clinical chemistry, hematology, and urinalysis test results
- physical examinations
- injection site assessment.

2.2.2. Exploratory Endpoints

The following exploratory objectives will be assessed:

- pain intensity and duration will be assessed by AUC, maximum pain intensity (E_{max}), and time of maximum pain intensity (tE_{max}), calculated using a capsaicin-evoked pain model. The exploratory endpoint of secondary hyperalgesia will be assessed by the area of secondary area of hyperalgesia (Part A only).
- continuous (24-hour) ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval (Part A).
- heat pain threshold measurements and heat pain tolerance measurements.

3. INVESTIGATIONAL PLAN

This will be a double-blind, randomized, placebo-controlled, single and multiple SC dose study conducted in 2 parts.

3.1. Overall Study Design and Plan

3.1.1. Part A

Part A will comprise a single-dose, sequential-group design. Overall, 44 healthy subjects will be studied in 8 groups. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety, tolerability, and PD (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, and A6 will attend a pre-screening visit for an intradermal capsaicin test (Section 3.4.2).

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (± 2 days), 10 (± 2 days), and 14 (± 2 days), and for a poststudy visit on Day 28 (± 2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (± 2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 7 (144 hours postdose) from the lower dose levels.

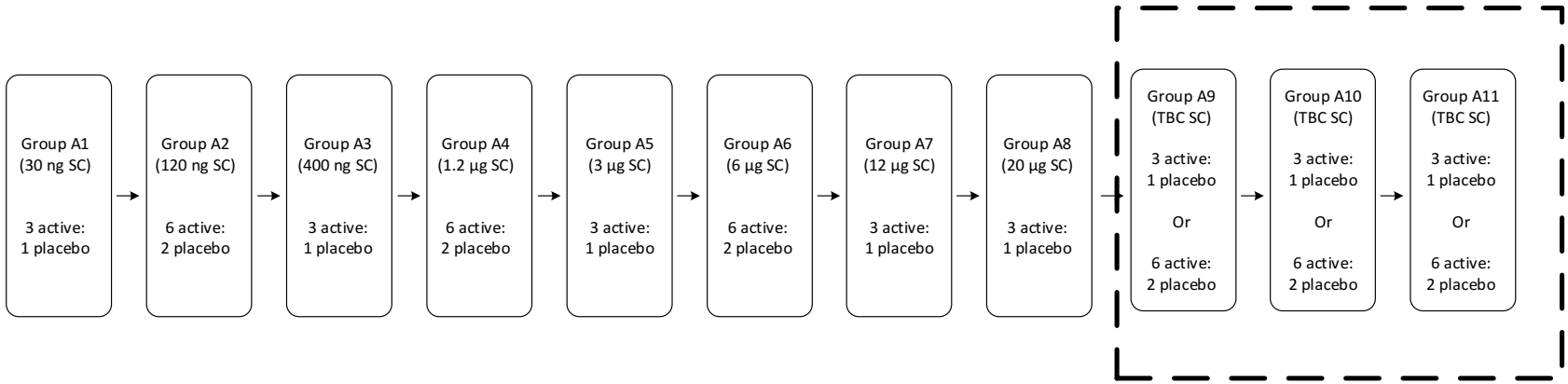
In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, and A6 will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.

Sentinel dosing will be employed for all groups in Part A. To maintain the blind in a 4-subject group, the first subject will be dosed 48 hours before the second subject, and the

second subject will be dosed 48 hours prior to the third and fourth subjects. In PD assessment groups, 2 subjects (1 active: 1 placebo) will be dosed 48 hours before the remaining 6 subjects (5 active: 1 placebo).

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic (Part A)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
Groups A9 to A11 may be included if required.
Three groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

3.1.2. Part B

Part B will comprise a multiple-dose, sequential-group study. Overall, 24 subjects will be studied in 3 groups (Groups B1 to B3), with each group consisting of 8 subjects. Up to 3 additional groups (24 subjects in total) may be included for further assessment of safety and tolerability (Section 3.3).

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15.

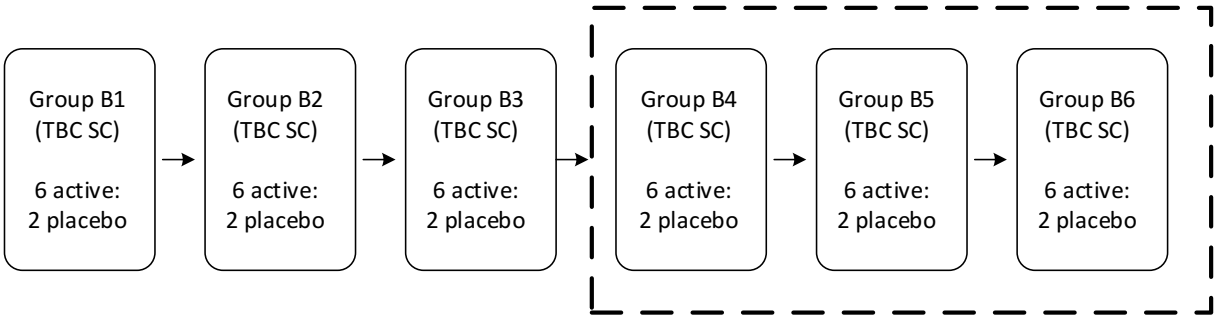
All subjects will return for non-residential visits on Days 18 (± 2 days), 22 (± 2 days), 25 (± 2 days), and 29 (± 2 days), and for a poststudy visit on Day 57 (± 2 days).

In each of Groups B1 to B3, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. There will be no sentinel dosing in Part B. For all subjects, a single subcutaneous dose will be administered on Days 1, 4, 7, 10, and 13. The dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 18 (120 hours post-final dose) from the lower dose levels. Part B may start after a review of the safety and tolerability for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

An overview of the study design is shown in Figure 2.

Figure 2: Study Schematic (Part B)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
All doses will be confirmed based on results of Part A.
Groups B4 to B6 will be included if required.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 12 weeks.

A Schedule of Assessments is presented in Appendix 6.

3.2. Start of Study and End of Study Definitions

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, and PD data, additional dose groups may be added to the study. Up to 3 further groups of 8 subjects (6 active: 2 placebo) may be included in Part A, and up to 3 additional groups of 8 subjects (6 active: 2 placebo) may be included in Part B. The requirement for additional groups will be agreed with the Sponsor and documented in the Trial Master File (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For both parts of the study, a sequential-group, ascending-dose design has been chosen for safety reasons as OLP-1002 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Subcutaneous doses have been chosen for both parts of the study, as this is the intended clinical route of administration.

Healthy male and female subjects will be recruited into this study. The inclusion of females of childbearing potential is in accordance with International Council for Harmonisation (ICH) M3, based on the short dosing duration (< 2 weeks).

In Part A, it is anticipated that groups of 4 subjects (3 active: 1 placebo) will be sufficient in order to determine safety and tolerability. In order to assess the PD effects of OLP-1002, 3 groups in Part A will include 8 subjects (6 active; 2 placebo). A full review of the safety and tolerability data from Part A will be performed to determine the dose regimen for Part B. Part B may start after a full review of all safety and tolerability data from Group A1 to A6. A review of PD data may also be performed, at the discretion of the Investigator. Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF.

Based upon the nonclinical data, the duration of a 28-day follow-up in Part A, and a 57-day follow-up in Part B is considered adequate to achieve the study objectives.

Pharmacokinetic analysis will not be conducted in this study. The bioanalytical method used for preclinical species has a lower limit of quantification (LLOQ) of 5 ng/mL. The increased sample volume possible from humans (compared to small animals) may afford an approximate 10-fold increase in sensitivity with possibly an additional 5-fold increase from the use of a more sensitive mass spectrometer. This could potentially deliver an LLOQ of around 0.1 ng/mL. It is apparent from the predicted plasma concentrations (see Section 3.5.2) that only a small number of samples around C_{max} at the highest doses would be quantifiable and that a conventional approach to pharmacokinetic will not achieve a full definition of the plasma concentration vs time profile or enable an estimation of the terminal phase. Thus, the

additional burden of sampling procedures would not be justified by the quality of the data which it would generate.

This study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Continuous ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing in Part A for groups consisting of 4 subjects will be such that there will be 48 hours between the first and second subjects, and 48 hours between the second and remaining 2 subjects in each group. For groups in Part A consisting of 8 subjects, 2 subjects (1 active: 1 placebo) will be dosed 48 hours prior to the remaining 6 subjects.

In Part B, all subjects in a group will be dosed on the same day. Accumulation of OLP-1002 is expected following multiple doses, based on the preclinical data, and will be taken into account when determining the doses for Part B (see Section 3.5.3).

In Parts A and B, there will be a minimum interval of a 10-minute gap between dosing subjects (when dosed on the same day). Continuation to dose the remaining subjects in a group will be at the Investigator's discretion.

3.4.2. Pharmacodynamic Assessment

Pharmacodynamic assessments will be conducted for subjects in Groups A2, A4, and A6.

Human experimental pain models using healthy volunteers can be used to assess the effect of a drug or treatment under controlled clinical conditions. Capsaicin is a vanilloid responsible for the pungent taste of hot peppers. In mammalian species, capsaicin-induced pain is mediated through Group C nerve fibers following activation of vanilloid 1 transient receptor potential (TRPV1) channels[5]. $Na_v1.7$ has been implicated in controlling neuropeptide release from C-fibers, and suppression of capsaicin-induced neurogenic flair has been demonstrated by an $NA_v1.7$ inhibitor[6].

Several studies have used intradermal capsaicin for human experimental pain studies[7,8]. It has been possible to demonstrate dose-dependent responses, with intradermal injections of 100 µg generally agreed to be the ideal dosage for these studies. Intradermal injection of capsaicin causes a brief stinging/burning pain at the injection site (spontaneous pain) followed by development of secondary hyperalgesia, which can be assessed using equipment such as Von Frey hairs. A study by Gazerani et al.[5] found that the response was site-specific

and while peak pain intensity and duration were greatest in the forehead it was found that areas of visible flare and secondary hyperalgesia were significantly larger in the forearm, making the forearm the most suitable site for experimentation.

Covance CRU, Leeds, UK in 2009 performed a validation study using intradermal capsaicin (Covance CRU Study: 9999-004) with between-subject and within-subject variability demonstrating that the assessments can be reliably conducted to assess pharmacological response.

For these reasons, it has been decided to:

- Measure both capsaicin-evoked pain and secondary hyperalgesia.
- Limit the number of capsaicin tests to 3 for each subject (pre-screening, baseline, and 48 hours postdose)
- Exclude subjects who have pain <3 or >9 (using a Visual Analogic Scale [VAS]) at the pre-screening visit from PD assessment groups.

3.5. Selection of Doses in the Study

3.5.1. Starting Dose

The rat has been identified as the most sensitive species in a 13-week SC toxicity study with a 4-week recovery phase (Covance study no. 8355564). The NOAEL was the 100 nmol/kg/dose (462.29 µg/kg/dose). This dose level resulted in C_{max} of 27.6 ng/mL and 24.9 ng/mL in males and females, respectively, and AUC_{0-24} of 174 ng.h/mL and 128 ng.h/mL in males and females, respectively[4]. As the exposure was lower in the female rats these data have been used to calculate the safety margins.

The dose of 462.29 µg/kg/dose corresponds to human equivalent doses (HEDs) of 74.8 µg/kg/dose, which gives a maximum recommended starting dose (MRSD) of 444 µg for a 60-kg human and thus a 15000-fold safety margin to the proposed starting dose of 30 ng and 22-fold margin to the proposed maximum dose of 20 µg. Additionally the NOAEL dose in the cynomolgus monkey was identified as 100 nmol/kg/dose (462.29 µg/kg/dose), which gives a higher HED of 150 µg/kg/dose.

In vivo, doses of 10 pmol/kg/dose (0.0462µg/kg/dose) or less were found to inhibit peripheral acute inflammatory pain. The equivalent human dose for a 60-kg human is 44 ng, thus a dose at which minimal biological effect is anticipated has been selected as the starting dose of 30 ng.

3.5.2. Exposure

Human exposures have been estimated from the pharmacokinetics in the cynomolgus monkey since a non-human primate represents the most closely related species. Approximately dose-proportional exposure was seen in the 13-week toxicity study (Covance study no. 8355565) and ^{14}C pharmacokinetic study (Covance study no. 8355568) over a dose range of approximately 1.1 to 100 nmol/kg (5.06 to 462.29 µg/kg)[4]. However, the lowest

dose (5.06 µg/kg) from the ^{14}C study has been used to estimate the human exposures as it is closest to the proposed human dose range and has the sufficient quantifiable data.

The assumptions made in the human exposure estimation were that human exposure would be similar to the cynomolgus monkey and that exposure would be linear with dose. Following a dose of 5.06 µg/kg in the cynomolgus monkey, the C_{max} was 1.96 ng/mL and $AUC_{0-\infty}$ was 12.7 ng.h/mL. The extrapolated exposures at the planned human doses are shown in Table 1 with margins calculated to the exposures at the NOAEL in the female rat.

Table 1: Estimated Human Exposure and Safety Margins to the NOAEL in the Female Rat for Single Dose Administration of OLP-1002

Human dose		Single dose to human		Safety margins for single dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\infty}$
0.03	0.000500	0.000194	0.00125	129000	102000
0.12	0.00200	0.000775	0.00502	32100	25500
0.4	0.00667	0.00258	0.0167	9640	7650
1.2	0.0200	0.0077	0.0502	3210	2550
3	0.0500	0.0194	0.125	1290	1020
6	0.100	0.0387	0.251	643	510
12	0.200	0.0775	0.502	321	255
20	0.333	0.129	0.837	193	153

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

The dosing interval currently anticipated for the multiple-ascending-dose part of this study is 72 hours or 96 hours. Thus the average dosing interval (82 hours) is similar to the half-life determined in the monkey ^{14}C study of 84 hours. Dosing at approximately once per half-life would be anticipated to result in accumulation of around 2-fold. However, higher levels of accumulation were observed (2.28-fold for C_{max} and 3.76-fold for AUC_{0-24}) on Day 88 at the top dose group (100 nmol/kg, 462.28 µg/kg) in the 13-week cynomologus monkey toxicity study following twice-weekly dosing (every 72 or 96 hours). Calculations were performed to estimate the likely human half-life using a standard 1-point allometric approach from the ^{14}C cynomolgus monkey pharmacokinetic study data. The exponents used were 0.75 for apparent total plasma clearance (CL/F) and 1 for apparent volume of distribution (V_z/F) values combined with the average body weight of the animal (3.1 kg) and scaling to a 60 kg human [9–11]. This resulted in a human half-life estimate of 180 h which in turn gave an accumulation estimate of 3.7-fold based upon a dosing interval of 82 h. This further supports the use of the greater than 2-fold accumulation from the 13-week cynomolgus study to estimate exposure following multiple dosing. Multiplication of the exposure estimates for the single ascending dose by 2.28 for C_{max} and 3.76 for AUC resulted in exposure estimates for multiple dosing presented in Table 2.

Table 2: Estimated Human Exposure and Safety Margin to the NOAEL in the Female Rat for Multiple Dose Administration of OLP-1002

Human dose		Multiple dose to human		Safety margins for multiple dose	
(µg)	(µg/kg)	Predicted C_{max} (ng/mL)	Predicted $AUC_{0-\infty}$ (ng.h/mL)	Margin to C_{max}	Margin to $AUC_{0-\tau,ss}$
0.03	0.000500	0.000442	0.00472	56000	27000
0.12	0.00200	0.00177	0.0189	14100	6800
0.4	0.00667	0.00589	0.0629	4230	2030
1.2	0.0200	0.017663	0.189	1410	680
3	0.0500	0.0442	0.472	560	270
6	0.100	0.0883	0.944	282	136
12	0.200	0.177	1.89	141	68
20	0.333	0.294	3.15	85	41
30	0.500	0.442	4.72	56	27

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration.

3.5.3. Proposed Doses

The proposed IMP dose levels for Parts A and B are shown in Table 3.

Table 3: Proposed Investigational Medicinal Product Dose Levels for Parts A and B

Study Part	Group	Dose (OLP-1002)
Part A	A1	30 ng or placebo
	A2	120 ng or placebo
	A3	400 ng or placebo
	A4	1.2 µg or placebo
	A5	3 µg or placebo
	A6	6 µg or placebo
	A7	12 µg or placebo
	A8	20 µg or placebo
	A9*	TBC or placebo
	A10*	TBC or placebo
	A11*	TBC or placebo
Part B	B1	TBC or placebo
	B2	TBC or placebo
	B3	TBC or placebo
	B4*	TBC or placebo
	B5*	TBC or placebo
	B6*	TBC or placebo

Abbreviations: TBC = to be confirmed
* groups to be included if required.

In Parts A and B, there should not be an increase of > 3-fold between dose levels above 120 ng.

For Part B, dose levels, dosing frequency, and dosing duration will be decided, in consultation with the Sponsor, on the basis of data from Part A of the study. Since predictions of human exposure of OLP-1002 suggest that OLP-1002 concentrations may be not be quantifiable and human data have been estimated from a single species, it is proposed that the highest dose in the multiple-ascending-dose part will be up to 50% of the highest dose in the single-ascending-dose part (ie, if the highest dose in the single-ascending-dose part is 20 µg, the highest dose in the multiple-ascending-dose part will be 10 µg). Therefore, if the predicted accumulation of 3.7-fold occurs, the highest exposure in the multiple-ascending-dose part will not exceed ~2-fold the maximum exposure in the single-ascending-dose part.

Details of all doses administered in Parts A and B of the study will be documented in the TMF.

3.6. Dose Escalation

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety and tolerability data up to Day 7 (144 hours postdose) from groups that received lower doses of OLP-1002.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 18 (120 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, and A6) have been reviewed from the previous lower dose group, such that data from a minimum of 5 subjects who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

The justification for this is as follows:

- The study drug is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.
- A minimum of 3 subjects receiving the active drug is considered sufficient to characterize the safety profile for OLP-1002.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarizing results from all available safety assessments, will be sent to the Sponsor and a dose-escalation meeting will occur prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PD data may also be reviewed on an ongoing basis. In the event of a disagreement between Sponsor and Investigator on the dose-escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

In Parts A and B, following consultation with the Sponsor, dose escalation will be stopped if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation.
- There is evidence of clinically significant increases in liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin) defined as 3 times the upper limit of normal in 3 or more subjects in a group (confirmed with repeat testing).
- QT interval corrected for heart rate using Fridericia's method (QTcF) increases > 60 msec compared to baseline (predose for Part A or Day 1 predose for Part B) and/or absolute QTcF values > 500 msec (confirmed by repeat measurement) in 2 or more subjects in a group.
- Tachycardia (> 150 beats/min) in the resting supine position (confirmed by 2 repeat measurements) on at least 2 occasions within a 24-hour interval in at least 2 subjects in a group.
- Severe hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) in the resting supine position (confirmed by 2 repeat measurements) on at least 2 occasions within a 24-hour interval in at least 2 subjects in a group.

If the sponsor deems it appropriate to resume dosing after the internal safety review, it can be done after the approval of a substantial protocol amendment.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Healthy male or females of any race, between 18 and 60 years of age, inclusive.
2. Body mass index (BMI) between 18.0 and 28.0 kg/m^2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, single 12-lead ECG (resting heart rate > 45 bpm and < 90 bpm), vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening as assessed by the Investigator (or designee).
4. Willing to abide by the contraception requirements as detailed in Appendix 4.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Any of the following:
    - QTcF > 450 ms confirmed by repeat measurement.
    - QRS duration > 110 ms confirmed by repeat measurement.
    - PR interval > 220 ms confirmed by repeat measurement.
    - findings which would make QTc measurements difficult or QTc data uninterpretable.
    - history of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
4. History of alcoholism or drug/chemical abuse within 1 year prior to Screening.
5. Alcohol consumption of > 21 units per week for males and >14 units per week for females. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
6. Positive alcohol breath test result or positive urine drug screen (confirmed by repeat) at Screening or Check-in.
7. Positive hepatitis panel and/or positive human immunodeficiency virus test (Appendix 2).
8. Active skin conditions such as dermatitis, allergy, eczema, psoriasis, or abnormal healing.
9. Tattoos, scars, or moles that in the opinion of the Investigator are likely to interfere with dosing or study assessments at any of the potential injection sites.
10. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days or 5 half-lives of the investigational product, whichever is longer, prior to Check-in.
11. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
12. Use or intend to use any prescription medications/products other than hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine

contraceptive concomitant medications within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).

13. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
14. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and/or Sponsor have given their prior consent.
15. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in.
16. Receipt of blood products within 60 days prior to Check-in.
17. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
18. Poor peripheral venous access.
19. Have previously completed or withdrawn from this study or any other study investigating OLP-1002, and have previously received the investigational product.
20. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
21. Part A – PD assessment groups only
    - Subjects considered non-acceptable responders to the intradermal capsaicin test at screening, defined as maximum VAS score of < 3.0 or > 9.0.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number at the time of their randomization. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A, Subjects 101, 102, etc., in Part B Subjects 201, 202, etc.). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancelation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

Vials of OLP-1002 Injection Solution 100 µg/mL (1.5 mL in 5-mL vials) and the Diluent for OLP-1002 Injection Solution (5 mL in 10-mL vials) will be supplied by the Sponsor, along with the batch/lot number and Certificate of Analysis. The Diluent for OLP-1002 Injection Solution will also be used as the Placebo formulation. A certificate of batch certification and release, authorized by a Qualified Person in the European Union (EU) will also be issued, by a Covance CRU Qualified Person, for each batch of IMP imported into the EU.

The IMPs will be stored according to the instructions on the label at the CRU in a location that is locked with restricted access.

Dose solutions (OLP-1002 Injection Solution diluted with the Diluent for OLP-1002 Injection Solution) will be prepared by Covance CRU Pharmacy staff in accordance with instructions provided in the Pharmacy Manual. The Placebo formulation will be the Diluent for OLP-1002 Injection Solution without further manipulation.

5.2. Study Treatment Administration

Subjects will be administered the IMP in numerical order. OLP-1002 will be administered by SC injection in the upper arm. If subcutaneous dosing of OLP-1002 in the upper arm is not possible, the subject may be dosed in the abdomen at the Investigator's discretion. For subjects in Groups A2, A4, and A6, dosing will be on the opposite arm to the intradermal capsaicin test.

5.3. Randomization

The randomization code will be produced by the statistics department at Covance using a computer-generated pseudo-random permutation procedure. In Part A, 1 subject in groups consisting of 4 subjects, and 2 subjects in groups consisting of 8 subjects, will be randomly assigned to receive placebo. In Part B, 2 subjects per group will be randomly assigned to receive placebo. All other subjects in a group will be randomized to receive OLP-1002.

Prior to the start of the study, a copy of the master randomization code will be supplied into the Covance CRU pharmacy staff (in sealed envelopes).

5.4. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The placebo solution will be identical in appearance to the OLP-1002.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomization code during the assembly procedure.

To maintain the blind, the Investigator will be provided with sealed randomization code-break envelopes for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety or to support dose-escalation decisions (in the event of possibly treatment-related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

All doses of IMP will be administered by suitably qualified study site staff.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record

will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription medications/products from 14 days prior to dosing until the Follow-up visit, and non-prescription medications/products from 7 days prior to dosing until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days), hormone-replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an AE. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for safety laboratory tests. On dosing days, subjects will receive a light breakfast approximately 2 hours prior to dosing. Meals will be provided as appropriate at other times and water will be freely available at all times.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Check-in until the Follow-up visit.

Xanthine-containing foods and beverages will not be allowed from 36 hours before Check-in until Discharge from the site. Xanthine-containing foods and beverages will also not be allowed form 36 hours before non-residential site visits.

Chili pepper/hot sauce will not be allowed for 48 hours prior to Check-in for all subjects. Subjects in Groups A2, A4, and A6 will not be allowed chili pepper/hot sauce for 48 hours prior to their pre-screening visit.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until Discharge. Following discharge, up to 2 units/day of alcohol are permitted until 36 hours before each non-residential visit and the Follow-up visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Check-in until the Follow-up visit.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 3 days before Check-in until the Follow-up visit and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit. Subjects should not be in receipt of blood products for 60 days prior to check-in.

6.6. Other Restrictions

Subjects in Groups A2, A4, and A6 will not be allowed to shower within 1 hour prior to the capsaicin-evoked pain tests at prescreening, predose, and postdose.

Subjects will not be allowed to apply moisturizing creams or oils to the dosing site within 1 hour prior to dosing, or to the assessment site within 1 hour prior to the capsaicin-evoked pain test.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- vital signs
- blood samples
- cardiac monitoring/ECG extractions
- any other procedures.

7.1. Pharmacodynamic Assessments

Capsaicin intradermal test will be performed for subjects in Groups A2, A4, and A6. Each subject will be tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).

7.1.1. Capsaicin-evoked Pain Model

The capsaicin model will be conducted by intradermal injection of capsaicin (100 µg in 100 µL of sterile saline containing 8% [w/w] Tween 80) into the skin of the anterior aspect of the forearm, midway between the elbow and the wrist. The bleb area (wheal) will be a sign of local plasma extravasation. An assessment of the pain intensity related to capsaicin injection will be estimated by repeated use of a VAS from injection to 5 minutes post-injection or until the pain intensity returned to zero. The AUC, E_{max}, and tE_{max} will be calculated and reported using dedicated software.

7.1.2. Secondary Hyperalgesia

The area of secondary hyperalgesia will be quantified with a 60-g weighted von Frey hair, by stimulating along 8 linear paths (4 vectors crossing at the location of the injection site) arranged vertically and horizontally around the stimulation site in 5-mm steps (starting approximately 6 cm away from the injection site). The area of secondary hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection.

7.2. Safety and Tolerability Assessments

Safety and tolerability assessments will be conducted at the times indicated in the Schedule of Assessments (Appendix 6). Timepoints may be adjusted based on an ongoing review of the data, and additional assessments may be conducted if deemed necessary by the Investigator or designee.

7.2.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion.

7.2.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 6. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6. For all female subjects, a follicle-stimulating hormone (FSH) test and pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.2.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Day 1 predose blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

Subjects must be supine for at least 5 minutes before blood pressure, pulse rate, and respiratory rate measurements.

7.2.4. Electrocardiogram

7.2.4.1. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value > 500 msec
- QTcF change from the mean baseline (Day 1 predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

Day 1 predose 12-lead ECGs will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.2.4.2. Continuous (24-hour) Electrocardiogram

At the times indicated in the Schedule of Assessments (Appendix 6), continuous (24-hour) ECGs will be performed.

Subjects will be supine for at least 10 minutes before the extraction timepoint and for 5 minutes from the start of each extraction timepoint. Each extraction will last for 5 minutes. Environmental distractions (eg, television, playing games, radio, conversation) should be avoided during the pre-ECG time window.

Continuous 24-hour ECGs are not planned for Part B of the study but may be implemented if any clinically significant findings are identified in the data from Part A.

7.2.5. Heat Pain Threshold Test

Heat pain threshold tests will be conducted at the times indicated in the Schedule of Assessments (Appendix 6).

A computer-controlled thermal sensory analyzer device will be used to measure the heat pain threshold and tolerance level of the subjects. The heat pain assessments will be conducted on the subject's thigh.

Heat Pain Threshold:

For heat pain threshold measurements, the thermode will be placed directly on the skin of the right thigh, within an area selected before the start of the experiment and defined by surgical marking. The thermode will have a baseline temperature of 32 °C, and will be programmed to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in their dominant hand, to indicate when the heat pain threshold (first sensation of heat pain) is reached by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Heat Pain Tolerance:

For heat pain tolerance measurements, the thermode will be placed within the same surgically marked skin area of the anterior side of the right thigh, which was used to assess heat pain threshold. The thermode will have a baseline temperature of 32 °C, and will be programmed

to gradually increase at a rate of 1.0 °C per second. The subject will be given a controller in their dominant hand, to indicate when the heat-evoked pain has reached an intensity that is no longer tolerable, by pushing a button. At that time, the test will be stopped and the temperature returned to baseline within 1 second. This process will be repeated a further 2 times, with an interval of at least 1 minute between measurements (from start to start). The computer will record the average value of 3 experiments.

Safety Precautions

As there is a risk that OLP-1002 may affect the heat pain threshold, Covance CRU will put appropriate safety measures in place to ensure that subjects are not exposed to extremes of temperature when taking a shower or consuming hot drinks. During the heat pain safety assessments, the cut-off temperature for either test is 53 °C in order to prevent skin injury.

7.2.6. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 6.

7.2.7. Body Weight and Height

Body weight (in underclothes) and height will be recorded at the times indicated in the Schedule of Assessments in Appendix 6. BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{body weight (kg)}}{(\text{height [m]})^2} \quad (\text{kg/m}^2)$$

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. In order to achieve PD endpoints in Part A, additional subjects will be included in 3 groups (8 subjects in total; 6 active: 2 placebo). Up to 3 additional groups may be added to Part A, consisting of either 4 subjects (3 active; 1 placebo) or 8 subjects (6 active; 2 placebo). Up to 3 additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).

8.2. Analysis Populations

8.2.1. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of study treatment OLP-1002 or placebo and for whom PD can be evaluated.

8.2.2. Safety Population

The safety population will include all subjects who received at least 1 dose of study treatment OLP-1002 or placebo and have at least 1 postdose safety assessment.

8.3. Pharmacodynamic Analyses

Pharmacodynamic parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned.

8.4. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- Mild: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but posing no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- Not Related: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- Unlikely Related: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- Related: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the investigational medicinal product (IMP) or study procedures at the Follow-up visit will be followed up, where possible,

until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of

hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the Clinical Research Unit (CRU). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Covance Drug Safety Services (DSS) Europe, Maidenhead, UK are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to DSS and the Sponsor immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Covance DSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the Safety Management Plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 2 working days of the initial notification to DSS. Drug Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Covance's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy reported by female subjects or

the female partners of male subjects should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Calcium Chloride Cholesterol Creatinine Direct bilirubin Gamma-glutamyl transferase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Total protein Urea	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[a]:	**Drug screen[b]:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test MDMA Alcohol breath test	Follicle-stimulating hormone[a] Serum pregnancy test (human chorionic gonadotropin)[a] Urine pregnancy test[c]

[a] Only analyzed at Screening.
[b] Only analyzed at Screening and Check-in.
[c] A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

Part A

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (excluding serology)	7.5	4	30
Serology	3.5	1	3.5
Total:			33.5

Part B

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations (excluding serology)	7.5	10	75
Serology	3.5	1	3.5
Total:			78.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject during the study will not exceed that donated during a standard blood donation (approximately 500 mL).

Appendix 4: Contraception Guidance

Definitions

Females of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Females of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use 2 methods (1 primary highly effective and 1 secondary method) of birth control from the time of signing the informed consent form until 90 days after the Follow-up visit. Primary highly effective methods of contraception include:

- surgical method performed at least 3 months prior to the Screening visit:
  - bilateral tubal ligation
  - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant eg, Implanon (as prescribed)
- hormonal or non-hormonal intrauterine device with appropriate re-insertion period (as prescribed)
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects can only choose a cervical cap or diaphragm if they have already had a prescription and fitting by their healthcare provider to ensure protocol requirements are met. Female subjects of childbearing potential should refrain from donation of ova from Check-in until 90 days after the Follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Check-in until 90 days after the Follow-up visit. Acceptable methods of contraception include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure® [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide
- vasectomised male subject (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success).

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the Follow-up visit. Male subjects are required to refrain from donation of sperm from Check-in until 90 days after the Follow-up visit.

Sexual Abstinence and Same-sex Relationships

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF until 90 days after the Follow-up visit.

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the Follow-up visit.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a

public registry, all identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Covance is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Covance electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled and randomized subject, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process will occur:

If the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator will submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor will have 60 days to respond with any requested revisions including, without limitation, the deletion of confidential information. The Investigator will act in good faith upon requested revisions, except the Investigator will delete any confidential information from such proposed publications. The Investigator will delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 6: Schedule of Assessments

Study Plan – Part A (Single Dose)

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Urine drugs of abuse screen		X	X							
Alcohol breath test		X	X							
Cotinine test		X	X							
Serology		X								
Hormone panel		X								
Urine pregnancy test[a]		X	X							X
Informed consent	X	X								
Study residency:										
Check-in			X							
Check-out					Day 3 (48 hours postdose)					
Non-residential visit	X	X				X	X	X	X	X
Study drug administration:					Day 1 (0 hours)					
Safety and tolerability:										
Adverse event recording		X	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording		X	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature		X			Predose, 1, 2, 4, 8, 24 (± 1 hour), and 48 hours postdose	X	X	X	X	X

	Pre-screening[d]	**Screening**	**Day -2**	**Day -1**	**Days 1 to 3**	**Day 4**	**Day 7 (± 2 days)**	**Day 10 (± 2 days)**	**Day 14 (± 2 days)**	**Poststudy (Day 28 ± 2 days)**
Supine 12-lead ECG		X			Predose, 4, 24 (± 1 hour) and 48 hours postdose		X		X	X
Continuous ECG extraction[b,c]				-24, -23.5, -23, -22.5, -22, -21.5, -21, -20, -18, -16, -12 hours	Day 1: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours					
Heat pain threshold test (heat pain threshold and heat pain tolerance)					Day 1: predose, 2, 4, 12, and 24 hours postdose (± 1 hour)					
Clinical chemistry, haematology, and urinalysis		X			48 hours postdose		X			X
Height and BMI		X								
Body weight		X	X							X
Physical examination		X								
Symptom-directed physical examination					Prior to discharge		X		X	X

	Pre-screening[d]	Screening	Day -2	Day -1	Days 1 to 3	Day 4	Day 7 (± 2 days)	Day 10 (± 2 days)	Day 14 (± 2 days)	Poststudy (Day 28 ± 2 days)
Injection site assessment					Predose, 1, 2, 4, 8, 24, 48 hours postdose		X		X	X
Pharmacodynamics[d]:										
Intradermal capsaicin test (capsaicin-evoked pain and secondary hyperalgesia measurement)	X		X		Day 2 (The area of secondary area of hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection)					

Abbreviations: BMI = body mass index; ECG = electrocardiogram.
[a] A positive urine pregnancy test result will be confirmed with a serum pregnancy test.
[b] All times are relative to dosing with OLP-1002.
[c] Continuous ECG recording may begin at approximately 25 hours before dosing to allow for checks to be completed prior to the first extraction timepoint and will continue for 24 hours postdose, ie, until after the last timepoint for ECG extraction (24 hours postdose). At timepoints for ECG extractions, subjects will be supinely resting for a total of 15 minutes (10-minute supine rest period, 5-minute extraction). Data will be archived for potential future analysis and will not be available for review during the study.
[d] Pharmacodynamic assessment groups only.

Study Plan – Part B (Multiple Dose)

	Screening	Day -1	Days 1-15	Day 18 (± 2 days)	Day 22 (± 2 days)	Day 25 (± 2 days)	Day 29 (± 2 days)	Poststudy (Day 57 ± 2 days)
Inclusion/exclusion criteria	X							
Demographic data	X							
Medical history	X							
Urine drugs of abuse screen	X	X						
Alcohol breath test	X	X						
Cotinine test	X	X						
Serology	X							
Hormone panel	X							
Urine pregnancy test[a]	X	X			X		X	X
Informed consent	X							
Study residency:								
Check-in		X						
Check-out			Day 15 (48 hours postdose)					
Non-residential visit	X			X	X	X	X	X
Study drug administration:			Days 1, 4, 7, 10, and 13					
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X
Concomitant medication recording	X	X	Ongoing	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate, and body temperature	X		Day 1: predose, 1, 2, 4 and 8 hours postdose Day 2, Day 4 (postdose), Day 5, Day 7 (postdose), Day 9, Day 10 (postdose), Day 12, Day 13: predose, 1, 2, 4 and 8 hours postdose, and Day 15	X	X	X	X	X

	Screening	Day -1	Days 1-15	Day 18	Day 22	Day 25	Day 29	Poststudy (Day 57 ± 2 days)
Heat pain threshold test (heat pain threshold and heat pain tolerance)	X		Day 1 and Day 13: predose, 1, 2, 4, 8, 24 hours postdose					
Supine 12-lead ECG	X		Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X
Clinical chemistry, haematology, and urinalysis	X	X	Days 2, 4, 7, 10, 13		X		X	X
Height and BMI	X							
Body weight	X	X						X
Physical examination	X							
Symptom-directed physical examination			Days 1, 4, 7, 10, 13		X		X	X
Injection site assessment			Day 1: predose and 4 hours postdose Day 4: predose and 4 hours postdose Day 7: predose and 4 hours postdose Day 10: predose and 4 hours postdose Day 13: predose and 4 hours postdose Day 15		X		X	X

Abbreviations: BMI = body mass index; ECG = electrocardiogram.
[a] Positive urine pregnancy test results will be confirmed with a serum pregnancy test.