CONFIDENTIAL

CLINICAL STUDY PROTOCOL

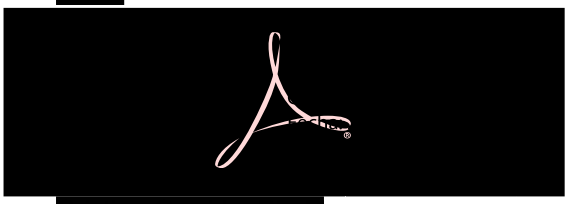
A Phase I, double-blind, randomized, placebo-controlled study to assess the safety and pharmacokinetics of ATL-001 (ciclopirox olamine) in healthy volunteers

Study code:	ATL001-PI-CEP	Study development phase:	Phase I
NCT number:	05647343	Investigational medicinal product:	ATL-001
		Indication:	N/A
Version:	4.0	Date:	13 December 2023
Atlas COO:	[redacted]		
Atlas CEO:	[redacted]		

1. SIGNATURES

This Clinical Study Protocol is approved by:

[redacted]



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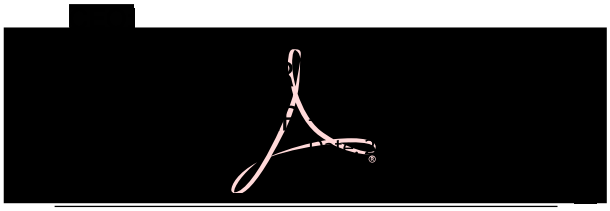

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1.1 PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY			
Document	**Date**	**Description of changes**	**Rationale**
Final Version 1.0	*27/07/2022*	Original Protocol	
Final Version 2.0	*24/08/2022*	• Initial dose change to 0.2 mg/kg. • Higher dose steps changed to 0.5, 1.0 and 2 mg/kg. • Number of arms changed from three to four. • revision of the DLT criteria. • revision of the stopping criteria. • definition of AE according to NCI-CTCAE. • Changes in the inclusion criteria.	*Response to FDA suggestions*
Final Version 3.0	*02/01/2023*	• NCT number included • Personnel roles assigned • Section 2-Synopsis: site contact details added • Section 2-Synopsis/Exclusion Criteria: updated for consistency with Section 9.6 of Protocol • Section 5 and 12.3: contact details added • Section 11.4.6: updates on the laboratory used for safety analyses • Section 16: removal of non-applicable signature • Minor edits	*Clarifications needed on Section 11.4.6 regarding Laboratory for safety analysis* *Updates on Protocol Synopsis due to discrepancies detected* *New information available regarding NCT number, site and team members contact details*
Final Version 4.0	*13/12/2023*	• Additional cohort and dose: Cohort 5 – 4 mg/ kg. Preparation (water volume) updated according to this higher dose • Minor edits and clarifications: ○ Clarification about Subject Diary delivery to the participants ○ Assessment of Uric acid crystals moved to Urinalysis section ○ eGFR (Inclusion Criteria) added as Screening assessment ○ Albumin and Total Protein listed separately for clarity ○ IMP Manufacturer for arm 5	*Inclusion of additional cohort*

		○ PK Data removed from Section 13.4 for consistency with Section 8.1 ○ Clarification on weight value used for dose calculation ○ Updates on Section 10.5 Blinding: Sponsor unblinding team, unblinding nurse and details on blinding break by pharmacovigilance personnel ○ Clarification about Screening assessments being required prior to dosing ○ Syringes references removed ○ Updates on Section 5. Administrative Structure	

2. SYNOPSIS

Name of the Sponsor/Company: Atlas Molecular Pharma S.L.	**Study Code:** ATL001-PI-CEP
Name of Investigational Medicinal Product: ATL-001	**NCT No.:** 05647343
Development Phase of the Study: Phase I	**Trial under an IND:** Yes (#154112)

TITLE OF THE STUDY:

A Phase I, double-blind, randomized, placebo-controlled study to assess the safety and pharmacokinetics of ATL-001 (ciclopirox olamine) in healthy volunteers

SHORT TITLE

Safety and pharmacokinetics of ATL-001 (ciclopirox olamine) in healthy volunteers

OBJECTIVES:

The primary objective of the study is to investigate the safety and tolerability of ATL-001 in healthy subjects.

The secondary objective is to determine the pharmacokinetics (PK) of ATL-001 in healthy subjects.

ENDPOINTS

Primary endpoints

- Incidence of adverse events (AEs) and of clinically relevant changes in vital signs values, electrocardiogram (ECG) data, physical examination and laboratory safety data for five different doses of ATL-001.

Secondary endpoints

- Derived pharmacokinetic parameters for ATL-001 including area under the plasma drug concentration versus time curve ($AUC_{(0\text{-last})}$, $AUC_{(0\text{-}12)}$, $AUC_{(0\text{-}24)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), apparent terminal half-life ($t_{1/2}$), apparent total body clearance (CL/F) and apparent volume of distribution (Vz/F), as appropriate.

OVERALL STUDY DESIGN:

This is a Phase I, double-blind, randomized, parallel-design, placebo-controlled, and dose escalation study to investigate the safety and PK of ATL-001 (ciclopirox olamine) in healthy subjects.

The study will consist of five sequentially recruited cohorts of 8 subjects each. Subjects will not be allowed to participate in more than one cohort. Five different ATL-001 doses will be tested along with their matching placebos: ATL-001 0.2 mg/kg, ATL-001 0.5 mg/kg, ATL-001 1 mg/kg, ATL-001 2 mg/kg and ATL-001 4 mg/kg. On the morning of Day 1 to Day 5, each subject will receive a single oral dose of ATL-001 or placebo administered as described below under fasting conditions.

For each cohort, subjects will be screened up to 30 days prior to the Baseline visit. All eligible subjects will be admitted to the study site on Day 1 (Baseline), for baseline assessments and to confirm their eligibility. They will remain domiciled until discharged on Day 2, after completion of the assessments and after receiving the Investigational Medicinal Product (IMP). All screening safety evaluation results must be available prior to dosing. Subjects will be randomized immediately prior to Day 1 IMP administration. At Day 5, subjects will be admitted again to the study site, where they will remain domiciled until discharged on Day 6 after completion of the assessments. Subjects will return to the study site, 3 days after their last IMP dose and 30 days after last IMP dose to undergo safety follow-up evaluations (FU-V1 and FU-V2).

For each cohort, the subjects will be randomized to receive ATL-001 (6 subjects/cohort) or to receive placebo (2 subjects/cohort). Each cohort will be sub-divided into 2 sub-cohorts:

- The first sub-cohort will have 2 sentinel subjects: one will be randomized to receive ATL-001 and one to receive placebo. Once these subjects complete their FU-V1 (3 days after the last IMP dose), the Sponsor and Principal Investigator (PI) will review all the available

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safety and tolerability data before deciding the inclusion of the remaining 6 subjects in the second sub-cohort.

- The second sub-cohort will include 6 additional subjects simultaneously: 5 randomized subjects to receive ATL-001 and 1 to receive placebo. Upon availability of the FU-V1 (3 days after the last IMP dose) data of all subjects, the Data and Safety Monitoring Board (DSMB) will review all available safety, tolerability, and will issue a recommendation for the next cohort to start. Only then the study may proceed with the next cohort for treatment administration after Sponsor decision. The same procedure will be followed for each subsequent cohort.

Depending on safety and tolerability data, the dose and administration schedule of ATL-001 might be recommended by the DSMB and changed after approval and authorization of the Sponsor. Additionally, the timing and number of safety assessments may be modified during the study after DSMB recommendation based on the results of emerging data. Any DSMB recommendation that would lead to a substantial amendment of the study protocol will be submitted to the Institutional Review Board (IRB) and Regulatory Authority (RA).

INVESTIGATIONAL MEDICINAL PRODUCT:

ATL-001 is a new oral formulation of ciclopirox olamine, including alginate and tocofersolan. Five different ATL-001 doses are planned to be used in this study along with their matching placebos: ATL-001 0.2 mg/kg, ATL-001 0.5 mg/kg, ATL-001 1 mg/kg, ATL-001 2 mg/kg and ATL-001 4 mg/kg. Each subject will receive once daily oral IMP administration for 5 days (i.e., total of 5 administrations of IMP).

NUMBER OF SUBJECTS:

The study will consist of five sequentially recruited cohorts of 8 subjects each, resulting in up to 40 randomized subjects.

NUMBER OF STUDY SITES:

Single-center study in the United States (CenExel HRI - Hassman Research Institute)

MAIN INCLUSION AND EXCLUSION CRITERIA:

Inclusion criteria

The subjects have to meet all of the following criteria to be eligible to enter the study:

1) Healthy male or female subjects 18 to 65 years of age, inclusive
2) Body mass index (BMI) within the range of 18.0 to 33.0 kg/m^2, inclusive, and a minimum weight of at least 50.0 and maximum weight of 100.0 kg at Screening
3) Estimated Glomerular Filtration Rate (eGFR) > 90 mL/min/1.73 m^2 at Screening
4) Female subjects of childbearing potential must be using and willing to continue using two medically acceptable contraceptive precautions from Screening and for at least 1 month after the last study drug administration. Medically acceptable forms of contraception include sexual abstinence [periodic abstinence (e.g., calendar, ovulation, symptothermal and post-ovulation methods) are not acceptable], combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), intrauterine devices (IUD), intrauterine hormone-releasing systems, and bilateral tubal ligation for subjects

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5) Female subjects of non-childbearing potential must be amenorrhoeic for at least 2 years or had a hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy (as determined by subject medical history)

6) Male subjects of reproductive potential with a partner(s) of childbearing potential must be using and willing to continue using two medically acceptable contraceptive precautions from Screening and for at least 1 month after the last study drug administration. Medically acceptable forms of contraception include abstinence, vasectomy, or male condom for subjects

7) Female subjects must have a negative pregnancy test

8) Must understand and provide written informed consent prior to the initiation of any protocol-specific procedures

9) Must be willing and able to abide by all study requirements and restrictions

Exclusion criteria

Subjects meeting any of the following criteria will not be permitted to enter the study:

1) Current drug or alcohol dependence (excluding caffeine), based on self-report, including subjects who have been in a drug rehabilitation program

2) Current smoker or a history of using tobacco products within 3 months prior to Screening

3) Clinically significant abnormalities on physical examination, medical history, 12-lead ECG (i.e., corrected QT interval (QTc) > 440 ms for male subjects and > 450 ms for female subjects), vital signs, or laboratory values, as judged by the investigator or designee

4) History or presence of any clinically significant illness (e.g., cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, musculoskeletal, or psychiatric) or any other condition, which in the opinion of the investigator would jeopardize the safety of the subject or the validity of the study results

5) Use of a non-prescription drug within 14 days prior to the first drug administration. Subjects who have taken over-the-counter medication may still be entered into the study, if in the opinion of the investigator or designee, the medication received will not interfere with the study procedures or data integrity or compromise the safety of the subject

6) Use of any prescription medications, recreational drugs, or natural health products (except vitamin or mineral supplements, acceptable forms of birth control, and hormone replacement) within 14 days prior to first drug administration or throughout the study, unless in the opinion of the investigator or designee, the product will not interfere with the study procedures or data integrity or compromise the safety of the subject

7) Use of any medication that interfere with the glucuronidation metabolic pathway within 14 days prior to first drug administration

8) Positive urine drug screen

9) Positive breath alcohol test. If a subject presents with positive breath alcohol test, the subject may be rescheduled at the discretion of the investigator or designee

10) Female subjects who are currently pregnant or lactating or who are planning to become pregnant within 60 days of last study drug administration

11) Known history of allergy or hypersensitivity to any component of the active drug or placebo

12) Positive for Hepatitis B, Hepatitis C, human immunodeficiency virus (HIV) or coronavirus disease (COVID)-19

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13) Treatment with any investigational drug within 30 days prior to first drug administration in the treatment phase

14) A subject who, in the opinion of the investigator or designee, is not considered to be suitable and is unlikely to comply with the study protocol for any reason

SAFETY/OTHER VARIABLES:

- PK parameters
- Demographic and Baseline Data
- Medical History
- Prior and Concomitant Medications
- AEs
- Physical examination
- Vital signs
- ECG
- Laboratory safety assessments

STATISTICAL METHODS:

A separate statistical analysis plan (SAP), which will provide more details of the statistical analysis outlined below, will be prepared and approved prior to unblinding the study data. No formal statistical hypothesis of the safety or tolerability are to be tested for this study.

There will be two analysis populations for this study:

- **Safety set:** All randomized subjects who receive at least one dose of the study medication regardless if they have or have not completed the study.
- **PK set:** All randomized subjects who received at least one dose of the study drug medication and have at least one valid PK measurement.

The analysis of safety and tolerability will be based on the Safety set. PK analysis will be based on the PK set.

Results of statistical analysis will be interpreted descriptively by treatment arm. All statistical models applied will foremost be used as tools for exploring treatment differences between treatment arms rather than formal testing of hypotheses. For this reason, corrections for multiple testing will not be applied in this study and, therefore, confidence intervals (CIs) or p-values indicating statistically significant differences between treatments should be interpreted as suggestive rather than evidence of differences.

No adjustment for covariates is planned for this study.

No missing value imputation will be done. All analyses will be conducted on observed data.

In general, data will be summarized by means of summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, first quartile (Q1), median, third quartile (Q3) and maximum value. Categorical data will be presented as counts and percentages. The data will be presented for each treatment group by visit.

Individual subject data will be listed.

STUDY PERIOD:

The anticipated study duration is about 11 months, with up to 66 days duration per subject.

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For each cohort, after a 30-day Screening period to establish subjects' eligibility, the subjects will be treated for 5 days (the treatment period) and followed by 30 days of observation and assessment of treatment outcomes (the follow-up period).	

2.1 Schedule of Activities (SoA)

Table 1. Schedule of Activities

	Screening period	Treatment period													Follow-up period	
	Screening visit	Hospital Admission												Hospital discharge†	FU-V1	FU-V2
Day	Day -30 to Day -1	Baseline (Day 1)	Day 1 and Day 5											Day 2 and Day 6	3 days after the last IMP dose	30 days after the last IMP dose
Assessment time		Pre-dose (0 h)	15 min (±5 min)	30 min (±5 min)	1 h (±10 min)	1:30 h (±10 min)	2 h (±10 min)	2:30 h (±15 min)	3 h (±15 min)	4 h (±30 min)	6 h (±30 min)	8 h (±30 min)	12 h (±30 min)	24 h (±30 min)		
Informed consent	X															
Inclusion/Exclusion criteria	X	X[1]														
Randomization		X														
Demographic data	X															
Medical history	X	X[2]													X[2]	X[2]
Physical examination	X	X					X							X	X	X
Vital signs[3]	X	X					X							X	X	X
Laboratory safety assessments[4]	X	X					X							X	X	X
Viral serology[5]	X															
Drug of abuse and alcohol screen	X	X														
Pregnancy test (females only)[6]	X	X[7]														

	Screening period	Treatment period													Follow-up period	
	Screening visit	Hospital Admission												Hospital discharge†	FU-V1	FU-V2
Day	Day -30 to Day -1	Baseline (Day 1)	Day 1 and Day 5											Day 2 and Day 6	3 days after the last IMP dose	30 days after the last IMP dose
Assessment time		Pre-dose (0 h)	15 min (±5 min)	30 min (±5 min)	1 h (±10 min)	1:30 h (±10 min)	2 h (±10 min)	2:30 h (±15 min)	3 h (±15 min)	4 h (±30 min)	6 h (±30 min)	8 h (±30 min)	12 h (±30 min)	24 h (±30 min)		
ECG	X	X					X							X	X	X
PK blood sampling		X[7]	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[8]	X[9]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ECG, electrocardiogram; FU-V, Follow-up Visit; h, hour; IMP, investigational medicinal product; min, minutes; PK, pharmacokinetics

† Subjects will be discharged at Day 2 and Day 6 after completing their assessments.

[1] Assessment of changes in inclusion/exclusion criteria

[2] Assessment of changes in the medical history

[3] Vital signs include: blood pressure, pulse rate and body temperature

[4] Laboratory safety assessments include: hematology, biochemistry, and urinalysis

[5] Viral serology will comprise human immunodeficiency virus (HIV) I and II, hepatitis B virus surface antigen (HBsAg) and hepatitis C virus testing, and coronavirus disease (COVID)-19 testing by polymerase chain reaction (PCR)

[6] Pregnancy testing of female subjects only. At screening pregnancy test will be done with using the blood sample; urine pregnancy test will be done on admission.

[7] Also pre-dose at Day 5

[8] Adverse events will be daily recorded by the subject in the subject diary and will not involve visit to the hospital.

[9] Pre-treatment-emergent events.

3. TABLE OF CONTENTS

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

4.1 List of Abbreviations

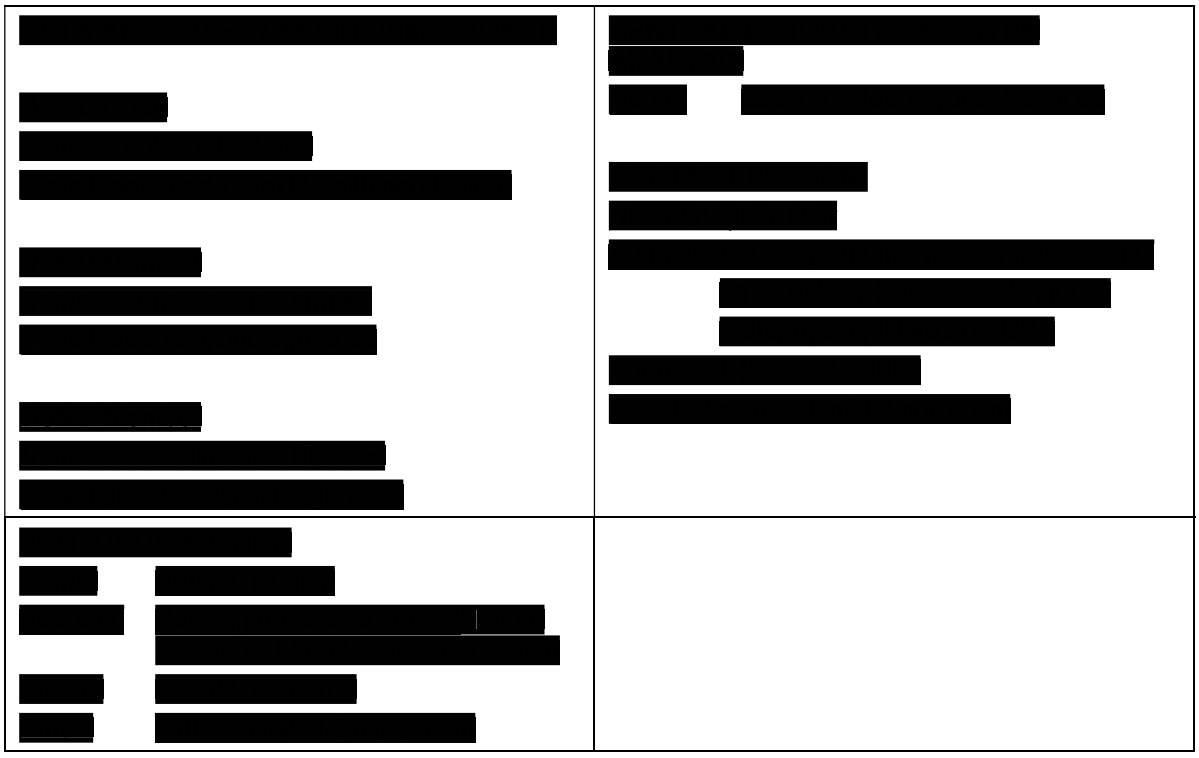
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
$AUC_{(0-12)}$	Area Under the Curve from time 0 to 12 hours after drug administration
$AUC_{(0-24)}$	Area Under the Curve from time 0 to 24 hours after drug administration
$AUC_{(0-last)}$	Area Under the Curve from time 0 to the time of the last measured concentration
CEP	Congenital Erythropoietic Porphyria
CI	Confidence Interval
CL/F	Total body clearance
C_{max}	Maximum observed plasma drug concentration
COVID	Coronavirus Disease 2019
CRO	Contract Research Organization
DLT	Dose-Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FU-V	Follow-Up Visit
GCP	Good Clinical Practice
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PK	Pharmacokinetics
QTcF	Corrected QT interval by Fredericia
RA	Regulatory Authority
RBMP	Risk-Based Monitoring Plan
rSDV	Remote Source Data Verification
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to Maximum observed plasma drug concentration
UROIIIS	Uroporphyrinogen III Synthase
US	United States
Vz/F	Volume of distribution
WHO	World Health Organization

4.2 Definition of Terms

Not applicable.

5. INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE



6. INTRODUCTION

6.1 Background

Porphyria is a group of disorders resulting from deficient activity of specific enzymes in the heme biosynthetic pathway [1]. Congenital erythropoietic porphyria (CEP), also known as Günther's disease, is a very rare inherited metabolic disorder resulting from a deficient activity of the enzyme uroporphyrinogen III synthase (UROIIIS), the fourth enzyme in the heme biosynthetic pathway. Due to the impaired function of this enzyme, excessive amounts of the non-physiologic and photoreactive porphyrinogens, uroporphyrinogen I and coproporphyrinogen I, accumulate particularly in the bone marrow, plasma, red blood cells, urine, teeth and bones. This in turn damages erythrocytes and elicits phototoxic reaction upon light exposure [2,3].

CEP is one of the least common porphyrias. Its prevalence has been estimated at 1 or less in 1,000,000. Until now, no clear sexual predominance has been noted [4]. It is inherited as an autosomal recessive disorder due to mutations in the UROIIIS gene. CEP has also been associated with a specific X-linked GATA1 mutation [2,3].

This disorder is characterized in most individuals by cutaneous photosensitivity and by hematologic abnormalities in affected individuals. The severity of clinical manifestations is heterogeneous among subjects. Usually, onset occurs at birth or early infancy and the first manifestation is pink-to-dark red discoloration of the urine. The predominant clinical characteristics of CEP include bullous cutaneous photosensitivity to visible light, progressive photomutilation of sun-exposed areas and hemolytic anemia. Hemolytic anemia is common and can range from mild to severe, with some affected individuals requiring chronic blood transfusions. In addition, subjects can develop corneal ulcers and scarring, erythrodontia, and bone loss and/or expansion of the bone marrow. The clinical spectrum of CEP, however, depends on the level of residual UROIIIS activity [2,3].

Currently, the management of CEP consists in strict avoidance of sun and light exposure, for example with the use of protective clothing, sunglasses and protective window filters. Wound care and use of topical antibiotics are indicated to prevent superinfections and osteolysis of opened blisters. Erythrocyte cell transfusions may be necessary to suppress hematopoiesis and decrease marrow production of the phototoxic porphyrins. There is no curative treatment other than bone marrow transplantation, an approach with some associated specific risks (e.g. toxicity problems derived from chemotherapy, infections derived from immunosuppression, transplant rejection or premature death) and which is only considered for the most severe cases [2,3].

6.2 Investigational Medicinal Product

Ciclopirox (6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone), often in the form of its olamine (2-aminoethanol) salt, is an off-patent synthetic antimicrobial agent which has previously been approved in the United States (US) as an anti-fungal topical treatment in the forms of gels, creams, lacquers and shampoos (anatomical therapeutic chemical [ATC] codes: D01AE14).

Ciclopirox olamine also acts as a pharmacological chaperone in CEP. By binding to UROIIIS, it stabilizes its structure and reduces its unfolding and degradation with time. Thus, ciclopirox olamine restores the protein levels of UROIIIS and its activity [5]. Considering that CEP is an ultra-rare disease, ciclopirox olamine was granted an orphan drug designation for the treatment of CEP by the US Food and Drug Administration (DRU-2018-6297, May 2018) and the European Medicines Agency (EMA/OD/186/17, January 2018) [6].

ATL-001 is a new formulation of ciclopirox olamine for oral administration, containing alginate and tocofersolan as excipients. The proposed indication for ATL-001 is the treatment of CEP.

The term investigational medicinal product (IMP) is used throughout the protocol to describe products received by the subjects as per the protocol design. In this study, five different ATL-001 doses will be tested along with their matching placebos. Thus, all of them are named as IMP in this protocol.

6.2.1 Summary of Non-Clinical Findings

6.2.1.1 Pre-Clinical Safety Data

Preclinical data of ciclopirox olamine have not shown prohibitive findings with respect to reproduction, toxicology, mutagenicity, carcinogenicity or phototoxicity.

A dermal carcinogenic study in mice of 1% and 5% ciclopirox olamine formulated in polyethylene glycol 400 applied to the intact skin, twice a week, for one year, followed by a six-month follow-up period was conducted. No tumors were observed in any mice at the application site. Overall incidence of neoplasms was similar among the treated and control groups. Moreover, there is no evidence that ciclopirox olamine is carcinogenic following a subcutaneous or oral administration to a number of animal species.

Ciclopirox olamine did not cause chromosomal damage or gene mutation in two mammalian assays or in several bacterial mutagen assays. In a battery of *in vitro* genotoxicity assays with ciclopirox free acid, one assay was weakly positive. Evidence of *in vitro* and *in vivo* assessments suggest that ciclopirox does not present a genotoxic hazard to humans.

Reproductive studies in mice, rats, rabbits and monkeys, at doses of ciclopirox olamine 10 times that of a topical human dose, revealed no significant evidence of impaired fertility or harm to the fetus. There is evidence that ciclopirox olamine crosses the placental barrier in animals.

6.2.1.2 Pharmacodynamic Effects

The effect of ciclopirox olamine on the activity of UROIIIS was demonstrated in cell-based and murine models of CEP. Ciclopirox targeted the enzyme at an allosteric site and did not affect its catalytic role. The drug restored enzymatic activity *in vitro* and *ex vivo* and was able to alleviate most clinical signs of CEP at subtoxic concentrations. Ciclopirox significantly reduced the levels of the toxic porphyrins, particularly uroporphyrin I and coproporphyrin I, in urine, red blood cells, and liver. Furthermore, it reduced splenomegaly, which is considered an indirect measure of reduction in circulating porphyrins [5,6].

6.2.1.3 Pharmacokinetic Properties

The pharmacokinetics (PK) of ciclopirox olamine was initially described during its development as an antifungal agent. Several studies were performed with oral administration, for instance, at a dose of 1 mg ciclopirox-14C-olamine/kg to rats, or in doses between 5-15 mg/kg to dogs. The results indicate that the compound is rapidly eliminated from blood (3–8 h). Most of the compound is renally excreted either unchanged or as glucuronide.

6.2.2 Summary of Clinical Findings

This is a first-in human study designed to assess the safety, tolerability, and PK of oral doses of ATL-001 in healthy adult volunteers, and thus, there is no available clinical research data to date on the IMP.

Nevertheless, other formulations of ciclopirox olamine have been previously orally administered to humans. A Phase I study assessed the tolerability and biologic activity of oral ciclopirox olamine in subjects with relapsed or refractory hematologic malignancy (NCT00990587). The drug was rapidly absorbed and cleared with a short half-life. Ciclopirox had a $t_{1/2}$ of less than 6 hours after both single and repeated administration. Despite the short apparent elimination $t_{1/2}$, the ciclopirox C_{max} values obtained following 80 mg/m^2 ciclopirox olamine once or four times daily exceeded 1 µM. Plasma concentrations of an inactive ciclopirox glucuronide metabolite were greater than those of ciclopirox. Grade 3 gastrointestinal dose-limiting toxicities (DLTs) and bowel inflammation were observed in 3 out of the 4 subjects in the cohort receiving 80 mg/m^2 four times daily. No DLT was observed at 40 mg/m^2 once daily [7].

6.3 Study Rationale

Non-clinical studies have demonstrated the medical plausibility of ciclopirox for the treatment of CEP, a very rare inherited metabolic disorder resulting from a deficient activity of UROIIIS. This drug acts as a pharmacological chaperone targeting UROIIIS and helps to restore its protein levels and activity.

Despite ciclopirox olamine is active at subtoxic concentrations and it has a fast turnover, acute gastrointestinal toxicity was observed due to the precipitation in the stomach of the active compound and subsequent accumulation in the intestine.

ATL-001 is a new oral formulation of ciclopirox olamine, including alginate and tocofersolan, currently under development for the treatment of subjects with CEP. This new oral formulation was developed

to improve the local tolerance of ciclopirox olamine, which otherwise induces dose-dependent gastrointestinal toxicity.

The present randomized, placebo-controlled, dose escalation, Phase I study aims to investigate the safety, tolerability and PK of ATL-001 at five different dose levels in healthy subjects.

The results of this study are intended to be used to identify appropriate and well tolerated doses of ATL-001 to be used in further studies.

6.4 Rationale for dose selection

The suggested selection of doses is based on the preclinical efficacy, safety and PK data. Efficacy studies in CEP mice suggest activity (defined as reduction of the circulating porphyrin levels in blood) at doses of 2,03 mg/kg (Human Equivalent Dose, HED). Importantly, efficacy is dose dependent. Moreover, PK and non-regulated toxicity studies in rodents (mice and rats) demonstrate that ATL formulation is safe at doses below 18 mg/kg in HED. These studies are further confirmed by a toxicity study in dog under Good Laboratory Practice (GLP-compliant) and further toxicity studies in rat, both at 9.2 mg/kg in HED. In any of these studies gastrointestinal toxicity or any adverse effect were observed. Nonetheless, taking into account that in a previous clinical experience, administration of ciclopirox olamine at 2.2 mg/kg four times daily in patients with hematological malignancies caused grade 3 gastrointestinal dose-limiting toxicities and bowel inflammation, we decided to start with a dose of 0.2 mg/kg, 10-fold lower than that causing toxicity in humans. Altogether, we propose testing 0.2, 0.5, 1, 2 and 4 mg/kg in the current phase trial. A treatment duration of 5 days was selected based on GLP-compliant Toxicokinetic study performed in dogs and considering that this time will suffice to observe the lack of gastrointestinal toxicity. In addition, the lack of toxicity (including gastrointestinal toxicity) observed in another GLP-compliant study, where dogs were daily administered with ATL-001 by the oral route during 28 days at 7.2 mg/kg (corresponding to a HED of 4 mg/kg), supports the safety of the dose of 4 mg/kg proposed for the 5th arm.

6.5 Potential Risks and Benefits

An analysis of potential risks for subjects participating in this study has been made. Identified risks and actions taken for their mitigation are summarized in Table 2.

Table 2. Identified Risk and Risk Minimization Actions

Identified Risk	Risk Minimization Actions
Gastrointestinal toxicity	Staggered approach to enrollment. The escalation to the next dose cohort should only occur after the safety and tolerability data from the current cohort is reviewed and deemed acceptable. Inclusion of DLTs and DSMB. Vital signs and physical examination monitoring.

DLT, dose-limiting toxicity; DSMB, Data and Safety Monitoring Board.

Risks and Benefits – Conclusion

The Sponsor considers the risk of serious adverse reactions to the IMP to be low, given the preventive actions taken and data from supporting animal studies. In conclusion, the named Sponsor believes the potential benefits of study participation outweigh the potential risks.

7. STUDY OBJECTIVES AND ENDPOINTS

Objective	*Endpoint*
Primary	
The primary objective of the study is to investigate the safety and tolerability of ATL-001 in healthy subjects	Incidence of adverse events (AEs) and of clinically relevant changes in vital signs values, electrocardiogram (ECG) data, physical examination and laboratory safety data for five different doses of ATL-001
Secondary	
To determine the PK of ATL-001 in healthy subjects	Derived pharmacokinetic parameters for ATL-001 including area under the plasma drug concentration versus time curve ($AUC_{(0\text{-last})}$, $AUC_{(0\text{-}12)}$, $AUC_{(0\text{-}24)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), apparent terminal half-life ($t_{1/2}$), apparent total body clearance (CL/F) and apparent volume of distribution (Vz/F), as appropriate

8. INVESTIGATIONAL PLAN

8.1 Study Design and Plan-Description

This is a Phase I, double-blind, randomized, parallel-design, placebo-controlled, and dose escalation study to investigate the safety and PK of ATL-001 (ciclopirox olamine) in healthy subjects.

The study will consist of five sequentially recruited cohorts of 8 subjects each, resulting in up to 40 randomized subjects. Subjects will not be allowed to participate in more than one cohort.

Five different ATL-001 doses will be tested along with their matching placebos: ATL-001 0.2 mg/kg, ATL-001 0.5 mg/kg, ATL-001 1 mg/kg, ATL-001 2 mg/kg and ATL-001 4 mg/kg (see Section 10.1.1). All of them are named as IMP in this protocol. On the morning of Day 1 to Day 5, each subject will receive a single oral dose of ATL-001 or placebo (i.e., total of 5 administrations of IMP) administered under fasting conditions (overnight fast; at least 10 hours) following the instructions below (Table 3).

The day of the first administration of the IMP will be considered Day 1 of the study.

Table 3. Study Cohorts Treatment Plan

Cohort	Investigational medicinal product	Route	Administration Days
1	ATL-001 0.2 mg/kg / Placebo	Oral	1, 2, 3, 4, 5
2	ATL-001 0.5 mg/kg / Placebo	Oral	1, 2, 3, 4, 5
3	ATL-001 1 mg/kg / Placebo	Oral	1, 2, 3, 4, 5
4	ATL-001 2 mg/kg / Placebo	Oral	1, 2, 3, 4, 5
5	ATL-001 4 mg/kg / Placebo	Oral	1, 2, 3, 4, 5

In order to maintain the double-blind study, the administration of the IMP must occur individually and separately, and in the absence of the physician responsible for the study. This is because the reaction after its administration could be easily distinguishable between placebo and ATL-001.

Given that the inclusion criteria established in Section 9.2 determine the selection of subjects with a minimum weight of 50 kg and a maximum of 100 kg, the volumes of IMP to be administered depending on the dosage are shown in Table 4. The corresponding volume in each case will be extracted using an FDA-recommended syringe (3-Piece Syringe Complies with international standards [ISO 7886-1]).

Table 4. Volumes of IMP to be Administered and the Corresponding Syringes

Cohort	Volume	Syringe
ATL-001 0.2 mg/kg / Placebo	From 0.5 mL to 1 mL	3 mL (scale - 0.1)
ATL-001 0.5 mg/kg / Placebo	From 1.5 mL to 3 mL	3 mL (scale - 0.1)
ATL-001 1 mg/kg / Placebo	From 2.5 mL to 5 mL	10 mL (scale – 0.2)
ATL-001 2 mg/kg / Placebo	From 5 mL to 10 mL	10 mL (scale – 0.2)
ATL-001 4 mg/kg / Placebo	From 10 mL to 20 mL	10 mL (scale – 0.2)

The volume to be administered will be extracted from the IMP container and will be deposited in a glass containing approximately 50-100 ml of water and to which 2-4 tablespoons of sugar have been added. The IMP will be stirred with a spoon and drunk in one gulp, if possible.

For each cohort, subjects will be screened up to 30 days prior to the Baseline visit. All eligible subjects will be admitted to the study site on Day 1 (Baseline), for baseline assessments and to confirm their eligibility. They will remain domiciled until discharged on Day 2, after completion of the assessments and after receiving the IMP. All screening safety evaluation results must be available prior to dosing. Subjects will be randomized immediately prior to Day 1 IMP administration. At Day 5, subjects will be admitted again to the study site, where they will remain domiciled until discharged on Day 6 after completion of the assessments. Subjects will return to the study site 3 days after their last IMP dose and 30 days after last IMP dose to undergo safety follow-up evaluations.

For each cohort, the subjects will be randomized to receive ATL-001 (6 subjects/cohort) or to receive placebo (2 subjects/cohort). Each cohort will be sub-divided into 2 sub-cohorts (Figure 1):

- The first sub-cohort will have 2 sentinel subjects: one will be randomized to receive ATL-001 and one to receive placebo. Once these subjects complete their follow-up visit 1 (FU-V1) (3 days after the last IMP dose), the Sponsor and Principal Investigator (PI) will review all the available safety and tolerability data before deciding the inclusion of the remaining 6 subjects in the second sub-cohort.
- The second sub-cohort will include 6 additional subjects simultaneously: 5 randomized subjects to receive ATL-001 and 1 to receive placebo. Upon availability of the FU-V1 (3 days after the last IMP dose) data of all subjects, the Data and Safety Monitoring Board (DSMB) will review all available safety, tolerability, and will issue a recommendation for the next cohort to start (Section 8.1.1). Only then the study may proceed with the next cohort for treatment administration after Sponsor decision. The same procedure will be followed for each subsequent cohort.

Depending on safety and tolerability data, the dose and administration schedule of ATL-001 might be recommended by the DSMB and changed after approval and authorization of the Sponsor (Section 8.1.1).

Additionally, the timing and number of safety assessments may be modified during the study after DSMB recommendation based on the results of emerging data (Section 8.1.1).

Any DSMB recommendation that would lead to a substantial amendment of the study protocol will be submitted to the Institutional Review Board (IRB) and Regulatory Authority (RA).

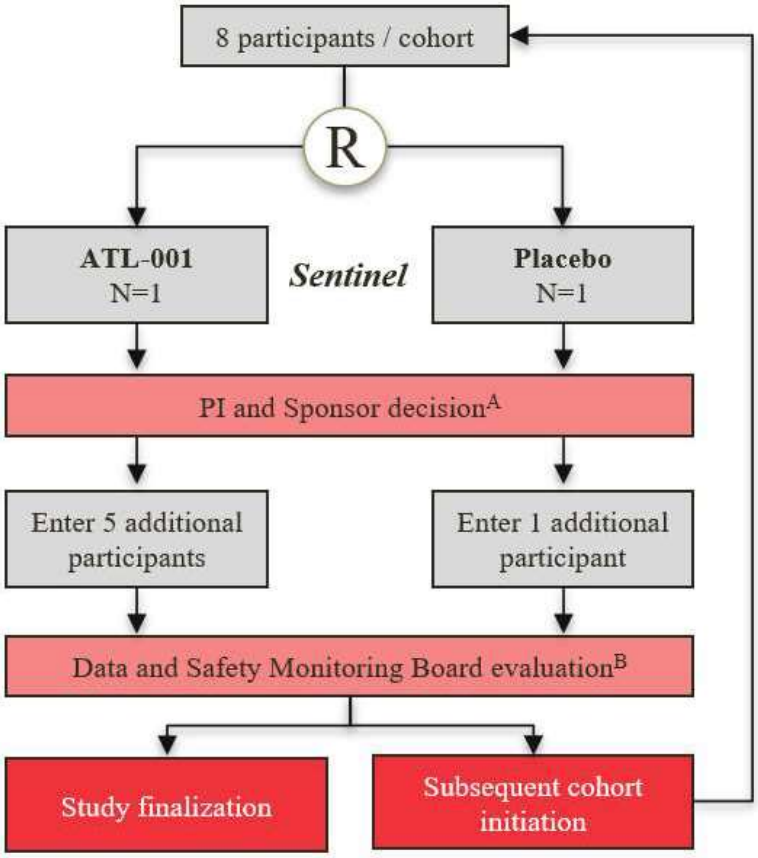


Figure 1. Overall Study Design

PI, Principal Investigator; R, Randomization.

[A] After sentinel subjects complete FU-V1 (3 days after the last IMP dose)
[B] Upon availability of the FU-V1 (3 days after the last IMP dose) data of all the cohort subjects. Final decision will be taken by the Sponsor based on DSMB recommendation

8.1.1 Data and Safety Monitoring Board Evaluation

The DSMB will issue recommendations regarding proceeding to each subsequent cohort based on all available safety, tolerability from all prior cohorts. The stopping rules described in Section 8.1.2 and the DLTs described in Section 8.1.3 will be considered.

Additionally, if the study level stopping rules described in Section 8.1.2 are met, the DSMB will automatically meet and issue a recommendation. The final decision on these actions will be taken by the Sponsor. The DSMB may meet additional times at the request of the PI or the Sponsor.

The DSMB may issue the following recommendations:

- To recommend the dosing start for the next cohort
- To change the dose for the next cohort*
- To repeat a dose that has been previously studied
- To change the administration schedule
- To add or change the timing of safety and/or PK assessments
- To recommend to the Sponsor that dosing should be stopped

*The DSMB proposed ATL-001 dose for a given cohort should not be superior to 8.1 mg/kg (see Appendix 1).

A DSMB charter will be produced by the Sponsor and will contain the following details:

- Committee members and requirements for quorum
- Data review requirements
- Process for informing the IRB and RA of any safety concerns, if appropriate
- Process for requesting additional pertinent information from the investigators
- Process for informing the investigators (and IRB/RA, if appropriate) of any decisions derived from the recommendations of the DSMB

8.1.2 Study-Level Stopping Rules

In case of any occurrence of one of the following criteria in one of the cohorts, the IMP administration will be temporarily stopped and the DSMB will meet to review the safety and tolerability data and issue a recommendation:

- 1 serious AE (SAE) in one subject that is considered to be at least possibly related to the IMP
- ≥2 subjects of one cohort (or 1 out of 2 sentinel subjects) reporting grade ≥2 or higher AEs that are considered to be at least possibly related to the IMP, regardless of attribution or relatedness to further enhance safety in this healthy volunteer study

If, after stopping the study, the Sponsor deem it appropriate to restart the study following a safety review by the DSMB, this will be done following approval of a substantial protocol amendment.

8.1.3 Dose-Limiting Toxicities

In case of any occurrence of one of the following criteria in one of the cohorts, no further dose escalation will be applied in subsequent cohorts:

- ≥ 1 subject of one cohort reporting grade ≥2 AEs up to FU-V1 (3 days after the last IMP dose)
- Corrected QT interval by Fredericia (QTcF) ≥500 ms and/or an increase of QTcF from baseline of ≥ 60 ms, confirmed by repeated ECGs, in at least 1 subject up to FU-V1 (3 days after the last IMP dose)

NOTE: Only toxicities with a clear-cut alternative explanation will be deemed non-DLT.

8.2 Study Procedures

8.2.1 Schedule of Study Events

The study assessments described in the sections below are presented in detail in Section 11.2 (PK assessments), Section 11.3 (demographic data and baseline characteristics) and Section 11.4 (safety assessments). Recording and reporting of AEs are described in detail in Section 12.

The timing of all study events is shown in Table 1.

The following points must be noted:

- If different assessments are scheduled for the same nominal time, then the assessments should occur in the following order whenever possible:
    1. 12-lead ECG and vital signs
    2. Blood draw
- The timing and number of planned study assessments, including safety or PK assessments may be altered during the course of the study based on newly available data (e.g., data from preceding cohorts) after DSMB recommendation (see Section 8.1.1).
- Any change in the timing or the addition of time points for any planned study assessment must be documented in a Note to File, which must be approved by the relevant Sponsor study team member and will be archived in the study Sponsor and site study files. This will not constitute a protocol amendment.

The day of the first administration of the IMP will be considered Day 1 of the study.

8.2.1.1 Screening Visit (Day -30 to Day -1)

At the Screening Visit, the following activities and assessments will be performed:

- Informed consent signature
- Assessment of inclusion/exclusion criteria
- Demographic data
- Medical history
- Physical examination
- Vital signs, including blood pressure, pulse rate and body temperature
- Laboratory safety assessments, including hematology, biochemistry and urinalysis
- Viral serology, comprising human immunodeficiency virus (HIV) I and II, HbsAg, hepatitis C virus and coronavirus disease (COVID)-19 polymerase chain reaction (PCR) testing
- Drug of abuse and alcohol screen
- Serum pregnancy test (for female subjects of childbearing potential only)
- ECG
- Concomitant medications
- AEs (pre-treatment-emergent events)

8.2.1.2 Treatment Period

After the Screening visit and confirmation of full eligibility, the subjects will receive the IMP once daily for 5 days. The first and last administration of the IMP (Day 1 and Day 5) will be performed at the hospital. At Day 2, prior to hospital discharge, the subject will be administered with the IMP. The other days (Day 3 to Day 4), treatment will be self-administered at home. During the first hospital admission (Day 1 to Day 2), subjects will be provided with the IMP to be administered daily from Day 3 to Day 4 and they will receive detailed instructions (see above, Section 8.1) on how to properly take and storage the medication. After the first and last administration of the IMP (Day 1 and Day 5) all subjects will be hospitalized for 24 hours. Subjects will be discharged at Day 2 and Day 6 after completing their assessments.

The timing of all study visits during this period is shown in Table 1.

8.2.1.2.1 Hospital admission (Day 1 to Day 2)

8.2.1.2.1.1 Day 1 (Baseline)

At Day 1 (Baseline), the following activities and assessments will be performed prior to IMP administration:

- Assessment of changes in inclusion/exclusion criteria
- Randomization
- Assessment of changes in the medical history
- Physical examination
- Vital signs, including blood pressure, pulse rate and body temperature
- Laboratory safety assessments, including hematology, biochemistry and urinalysis
- Drug of abuse and alcohol screen
- Urine pregnancy test (for female subjects of childbearing potential only)
- ECG
- PK blood sampling (0 min or pre-dose).

- Concomitant medications
- AEs (pre-treatment-emergent events)

After performing all the previous assessments, the IMP will be administered and the subjects will remain in the hospital for 24 hours. During Day 1, the following additional activities and assessments will be performed:

- Physical examination (2 hours after the first IMP dose)
- Vital signs, including blood pressure, pulse rate and body temperature (2 hours after the first IMP dose)
- Laboratory safety assessments, including hematology, biochemistry and urinalysis (2 hours after the first IMP dose)
- ECG (2 hours after the first IMP dose)
- PK blood sampling (15 min, 30 min, 1 hour, 1:30 hours, 2 hours, 2:30 hours, 3 hours, 4 hours, 6 hours, 8 hours and 12 hours after the first IMP dose)
- Concomitant medications
- AEs

8.2.1.2.1.2 Day 2

Subjects will be discharged at Day 2 after completing their assessments and after receiving the IMP. At Day 2 (24 hours after the first IMP dose), the following activities and assessments will be performed:

- Physical examination
- Vital signs, including blood pressure, pulse rate and body temperature
- Laboratory safety assessments, including hematology, biochemistry and urinalysis
- ECG
- PK blood sampling
- Concomitant medications
- AEs

Prior to hospital discharge (and after the performance of the activities and assessments listed above), the subjects will be administered with the IMP.

8.2.1.2.1.3 Day 3 to Day 4

Treatment will be self-administered at home once daily following the investigator instructions. No site visits are planned from Day 3 to Day 4. During this period of time, subjects will record daily AEs and IMP administrations in the subject diary.

8.2.1.2.2 Hospital admission (Day 5 to Day 6)

8.2.1.2.2.1 Day 5

At Day 5, the following activities and assessments will be performed prior to IMP administration:

- Urine pregnancy test (for female subjects of childbearing potential only)
- PK blood sampling (0 min or pre-dose)

After performing all the previous assessments, the IMP will be administered, and the subjects will remain in the hospital for 24 hours. During Day 5, the following activities and assessments will be performed after IMP administration:

- Physical examination (2 hours after the last IMP dose)
- Vital signs, including blood pressure, pulse rate and body temperature (2 hours after the last IMP dose)

- Laboratory safety assessments, including hematology, biochemistry and urinalysis (2 hours after the last IMP dose)
- ECG (2 hours after the last IMP dose)
- PK blood sampling (15 min, 30 min, 1 hour, 1:30 hours, 2 hours, 2:30 hours, 3 hours, 4 hours, 6 hours, 8 hours and 12 hours after the last IMP dose)
- Concomitant medications
- AEs

8.2.1.2.2.2 Day 6

Subjects will be discharged at Day 6 after completing their assessments. At Day 6 (24 hours after the last IMP dose), the following activities and assessments will be performed:

- Physical examination
- Vital signs, including blood pressure, pulse rate and body temperature
- Laboratory safety assessments, including hematology, biochemistry and urinalysis
- ECG
- PK blood sampling
- Concomitant medications
- AEs

8.2.1.3 Follow-Up Period

The follow-up period will include 2 visits, one scheduled 3 days after the last IMP dose and one scheduled 30 days after the last IMP dose.

8.2.1.3.1 FU-V1 (3 days after the last IMP dose)

At FU-V1 the following activities and assessments will be performed:

- Assessment of changes in the medical history
- Physical examination
- Vital signs, including blood pressure, pulse rate and body temperature
- Laboratory safety assessments, including hematology, biochemistry, and urinalysis
- ECG
- Concomitant medications
- AEs

8.2.1.3.2 FU-V2 (30 days after the last IMP dose)

At FU-V2 the following activities and assessments will be performed:

- Assessment of changes in the medical history
- Physical examination
- Vital signs, including blood pressure, pulse rate and body temperature
- Laboratory safety assessments, including hematology, biochemistry and urinalysis
- ECG
- Concomitant medications
- AEs

8.3 Discussion of Study Design, Including the Choice of Control Groups

This is a Phase I, double-blind, randomized, parallel-design, placebo-controlled study with a dose escalation design. It will be performed in healthy subjects who will receive treatment with oral ATL-001 or placebo once daily for 5 days. Healthy subjects were chosen for this study to avoid confounding factors from the disease or concomitant drugs in subjects with CEP that may hinder the evaluation of safety. Additionally, ethical considerations dictate exploration of safety and tolerability in healthy subjects first as subjects with CEP may be more vulnerable to side effects caused by the compound. Full details on study design are presented in Section 8.1.

ATL-001 is a new oral formulation of ciclopirox olamine, including alginate and tocofersolan, currently under development for the treatment of subjects with CEP. This new oral formulation was developed to improve the local tolerance of ciclopirox olamine, which otherwise induces dose-dependent gastrointestinal toxicity. ATL-001 has been studied *in vitro* and *in vivo*, and its safety profile has been found to be acceptable for initiating this trial. For information on ATL-001 non-clinical pharmacology, PK and toxicology as well as relevant disease background information, please refer to Section 6.2 and to the Investigator's Brochure.

The assessment of the expected benefits and risks of the current Phase I study is based on the study design and risk-minimization measures as well as the safety profile in pre-clinical studies, including toxicology assessments, and on predictions of the activity of ATL-001 in the subjects as derived from the comprehensive pre-clinical pharmacological data package.

The Sponsor has designed the study in such a way that the safety of ATL-001 can be investigated while keeping potential risks for the subjects to a minimum (see Section 6.5). Further, the dose escalation design ensures that the next dose cohort only will only occur after the safety and tolerability data from the prior cohort is reviewed and deemed acceptable.

The study is placebo controlled to provide a comparison group and to account for the placebo effect.

8.4 Study Period

The anticipated study duration is about 11 months, with up to 66 days duration per subject.

For each cohort, after a 30-day Screening period to establish subjects' eligibility, the subjects will be treated for 5 days (the treatment period) and followed by 30 days of observation and assessment of treatment outcomes (the follow-up period).

8.5 End of Study

The end of study is defined as the date of the last subject's last visit. The study will be completed after the last subject has performed the safety follow-up 30 days after the last IMP administration (FU-V2).

The Sponsor may discontinue the complete study at any time, for ethical or scientific reasons. The PI is entitled at any time to stop the study due to medical reasons. In such a case, the PI should consult the Sponsor at the earliest opportunity.

9. SELECTION OF STUDY POPULATION

9.1 Number of Subjects

The study will consist of five sequentially recruited cohorts of 8 subjects each, resulting in up to 40 randomized subjects. Sample size considerations are detailed in Section 13.2.

9.2 Inclusion Criteria

The subjects have to meet all of the following criteria to be eligible to enter the study:

1) Healthy male or female subjects 18 to 65 years of age, inclusive
2) Body mass index (BMI) within the range of 18.0 to 33.0 kg/m^2, inclusive, and a minimum weight of at least 50.0 kg and maximum weight of 100.0 kg at Screening
3) Estimated Glomerular Filtration Rate (eGFR) > 90 mL/min/1.73 m^2 at Screening
4) Female subjects of childbearing potential must be using and willing to continue using two medically acceptable contraceptive precautions from Screening and for at least 1 month after the last study drug administration. Medically acceptable forms of contraception include sexual abstinence [periodic abstinence (e.g., calendar, ovulation, symptothermal and post-ovulation methods) are not acceptable], combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), intrauterine devices (IUD), intrauterine hormone-releasing systems, and bilateral tubal ligation for subjects
5) Female subjects of non-childbearing potential must be amenorrhoeic for at least 2 years or had a hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy (as determined by subject medical history)
6) Male subjects of reproductive potential with a partner(s) of childbearing potential, must be using and willing to continue using two medically acceptable contraceptive precautions from Screening and for at least 1 month after the last study drug administration. Medically acceptable forms of contraception include abstinence, vasectomy, or male condom for subjects
7) Female subjects must have a negative pregnancy test
8) Must understand and provide written informed consent prior to the initiation of any protocol-specific procedures
9) Must be willing and able to abide by all study requirements and restrictions

9.3 Exclusion Criteria

Subjects meeting any of the following criteria will not be permitted to enter the study:

1) Current drug or alcohol dependence (excluding caffeine), based on self-report, including subjects who have been in a drug rehabilitation program
2) Current smoker or a history of using tobacco products within 3 months prior to Screening
3) Clinically significant abnormalities on physical examination, medical history, 12-lead ECG (i.e., QTc > 440 ms for male subjects and > 450 ms for female subjects), vital signs, or laboratory values, as judged by the investigator or designee
4) History or presence of any clinically significant illness (e.g., cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, musculoskeletal, or psychiatric) or any other condition, which in the opinion of the investigator would jeopardize the safety of the subject or the validity of the study results
5) Use of a non-prescription drug within 14 days prior to the first drug administration. Subjects who have taken over-the-counter medication may still be entered into the study, if in the opinion of the investigator or designee, the medication received will not interfere with the study procedures or data integrity or compromise the safety of the subject
6) Use of any prescription medications, recreational drugs, or natural health products (except vitamin or mineral supplements, acceptable forms of birth control, and hormone replacement) within 14 days prior to first drug administration or throughout the study, unless in the opinion of the

investigator or designee, the product will not interfere with the study procedures or data integrity or compromise the safety of the subject

7) Use of any medication that interfere with the glucuronidation metabolic pathway within 14 days prior to first drug administration
8) Positive urine drug screen
9) Positive breath alcohol test. If a subject presents with positive breath alcohol test, the subject may be rescheduled at the discretion of the investigator or designee
10) Female subjects who are currently pregnant or lactating or who are planning to become pregnant within 60 days of last study drug administration
11) Known history of allergy or hypersensitivity to any component of the active drug or placebo
12) Positive for Hepatitis B, Hepatitis C, HIV or COVID-19
13) Treatment with any investigational drug within 30 days prior to first drug administration in the treatment phase
14) A subject who, in the opinion of the investigator or designee, is not considered to be suitable and is unlikely to comply with the study protocol for any reason

9.4 Discontinuation/ Withdrawal Criteria

9.4.1 Withdrawal from the Study

Subjects are free to discontinue their participation in the study at any time without having to specify their reasons. Furthermore, subjects may be withdrawn from the study at any time, if deemed appropriate by the Investigator.

Potential reasons for withdrawal of subjects from this study are:

- Refuses to cooperate
- Experiences relevant signs or symptoms affecting subject safety
- Presents hypersensitivity reactions to the IMP
- The decision of a subject to withdraw from the study (including if the subject withdraws informed consent)
- Requires a medication that is prohibited by the protocol (see Section 10.6.2)
- Does not complete the study as outlined in the study protocol
- Is lost to follow-up

The reason and date the subject is withdrawn from the study will be documented in the electronic case report form (eCRF) (e.g., lost to follow-up, consent withdrawn, AEs, etc.). If a subject is withdrawn from the study, the Investigator should attempt to complete all discharge procedures. All AEs should be followed up according to Section 12.

If the subject withdraws consent or he/she is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses, unless this is prohibited by local regulations. The Investigator must document the withdrawal in the site study records.

In case of a withdrawn subject from the study, he/she may be replaced with another subject at the Sponsor's discretion. The replacement subject will be assigned to the same regimen dosage.

9.4.2 Withdrawal from Treatment

Subjects may voluntarily discontinue treatment with the IMP for any reason at any time. Subjects may be also withdrawn from the IMP at any time, if deemed necessary by the Investigator.

Potential reasons for withdrawal of subjects from the study treatment are:

- Occurrence of an AE of severe intensity (grade ≥3) which does not justify the continuation of the study treatment, or a SAE that will be judged by the Investigator as at least possibly drug-related

- Use of non-permitted concomitant medications (see Section 10.6.2)
- The decision of a subject to withdraw from the treatment
- Discontinuation of contraceptives during the treatment period
- Pregnancy

Subjects who discontinue treatment with the IMP should not be considered withdrawn from the study. They should return for follow-up visits. If subjects fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, and letter) should be made by the Investigator to contact them.

In case of a subject discontinuing the study treatment, he/she may be replaced with another subject, at the Sponsor's discretion. The replacement subject will be assigned to the same regimen dosage.

9.4.3 Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the site for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9.5 Premature Termination of the Study

The Investigator or the Sponsor may terminate this study prematurely for any reasonable cause. The IRB and Ras should be informed promptly.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study, or potential study subjects
- A decision on the part of the Sponsor to suspend or discontinue development of the IMP

If the RA obtains information that raises doubts about the safety or scientific validity of the clinical study, the RA can suspend or prohibit the study.

If the study is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects.

10. TREATMENT OF SUBJECTS

10.1 Investigational Medicinal Products

10.1.1 Identity of Investigational Medicinal Products

The product name is referred to as ATL-001. ATL-001, ciclopirox olamine oral solution, 20 mg/ml is a new oral formulation of ciclopirox.

Ciclopirox, including its salt form ciclopirox olamine, is an off-patent synthetic antimicrobial agent which has previously been approved in the US as an anti-fungal topical treatment (in the forms of gels, creams, lacquers and shampoos) for infections (ATC code: D01AE14).

ATL-001 is a new formulation of ciclopirox olamine for oral administration, containing alginate and tocofersolan as excipients (Table 5). The composition of the placebo will be the same as ATL-001 but without the drug substance. The proposed indication for ATL-001 is the treatment of CEP. It is planned to be administered orally, once daily as a chronic treatment.

Table 5. Composition of ATL-001

Substance Name Regulatory	Classification	Amount (100 mL of Syrup)
Ciclopirox Olamine	Drug Substance	2000.0 mg
Benzyl alcohol	Preservative	2092.0 mg
Sodium Alginate	Excipient	3000.0 mg
Tocofersolan	Excipient	5000.0 mg
Flavor strawberry	Excipient	100.0 mg
Colorant (Erythrosine)	Excipient	2.8 mg
Water	Solvent	q.s. 100 mL

Five different ATL-001 doses are planned to be used in this study along with their matching placebos: ATL-001 0.2 mg/kg, ATL-001 0.5 mg/kg, ATL-001 1 mg/kg, ATL-001 2 mg/kg and ATL-001 4 mg/kg. Each subject will receive once daily oral IMP administration for 5 days (i.e., total of 6 administrations of IMP). The details of the IMPs for Cohort 1, Cohort 2, Cohort 3, Cohort 4 and Cohort 5 are given in Table 6, Table 7,Table 8, Table 9 and Table 10, respectively.

Table 6. Identity of Investigational Medicinal Products (Cohort 1)

Investigational medicinal product	Pharmaceutical form	Dose	Route of administration	Manufacturer
ATL-001	Liquid syrup	0.2 mg/kg	Oral	Polypeptide Therapeutic Solutions
Placebo	Liquid syrup	Not applicable	Oral	Polypeptide Therapeutic Solutions

Table 7. Identity of Investigational Medicinal Products (Cohort 2)

Investigational medicinal product	Pharmaceutical form	Dose	Route of administration	Manufacturer
ATL-001	Liquid syrup	0.5 mg/kg	Oral	Polypeptide Therapeutic Solutions
Placebo	Liquid syrup	Not applicable	Oral	Polypeptide Therapeutic Solutions

Table 8. Identity of Investigational Medicinal Products (Cohort 3)

Investigational medicinal product	Pharmaceutical form	Dose	Route of administration	Manufacturer
ATL-001	Liquid syrup	1 mg/kg	Oral	Polypeptide Therapeutic Solutions
Placebo	Liquid syrup	Not applicable	Oral	Polypeptide Therapeutic Solutions

Table 9. Identity of Investigational Medicinal Products (Cohort 4)

Investigational medicinal product	Pharmaceutical form	Dose	Route of administration	Manufacturer
ATL-001	Liquid syrup	2 mg/kg	Oral	Polypeptide Therapeutic Solutions
Placebo	Liquid syrup	Not applicable	Oral	Polypeptide Therapeutic Solutions

Table 10. Identity of Investigational Medicinal Products (Cohort 5)

Investigational medicinal product	Pharmaceutical form	Dose	Route of administration	Manufacturer
ATL-001	Liquid syrup	4 mg/kg	Oral	Recipharm
Placebo	Liquid syrup	Not applicable	Oral	Recipharm

10.1.2 Packaging and Labelling of Investigational Medicinal Product(s)

The Sponsor will supply the study medication labelled and packaged for this study.

All packaging and labelling as well as the production of study medication will be in accordance with EudraLex volume 4, Annex 13 “Good manufacturing practices for Medicinal products for human and veterinary use” and applicable local regulatory requirements.

10.1.3 Storage and Handling of Investigational Medicinal Product(s)

Only subjects enrolled in the study may receive the IMP and only authorized site staff may supply the IMP. The IMP supplies must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The Investigator and study staff must adhere to Good Clinical Practice (GCP) guidelines, as well as local or regional requirements. Under no circumstances will the Investigator allow the IMP to be used other than as directed by this protocol.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

The IMPs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the designated personnel have access. Upon arrival of IMPs at the site, site personnel should check for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the Clinical Trial Monitor upon discovery. Upon receipt, all IMPs must be stored according to the instructions specified on the labels. The recommended storage conditions for the IMP are between 2-8 ºC. Clinical supplies are to be dispensed only in accordance with the protocol.

Refer to Pharmacy Manual with details on storage and handling of IMPs. Storage and use conditions will be also clearly detailed in a separated “Instruction for administration” document.

10.2 Method of Assigning Subjects to Treatment Groups

At each investigated cohort, subjects will be randomized in the ratio of 6 active treatments to 2 placebos (3:1). For safety reasons, the subjects of each cohort will be divided in 2 sub-cohorts with 2 sentinel subjects in the first sub-cohort and 6 additional subjects in the second sub-cohort (see Section 8.1). The randomization schedule will be designed so that in each sub-cohort there will be 1 subject scheduled to receive placebo.

The randomization list will be performed by someone not directly enrolled in the research team. SAS software version 9.4 or higher will be used. The disclosure of the randomization schedule will be done at the end of the study or in case it is needed to provide convenient medical care to any subject due to AEs.

Following confirmation of eligibility, subjects will be assigned a subject randomization number at Baseline using an Interactive Response Technology (IRT) system in the order in which they are randomized in the study.

Only subjects receiving an IMP administration will receive a randomization number. Subjects who replace a discontinued subject will receive the same administration as the discontinued subject. This subject will receive a number that refers to the number of the subject that is being replaced.

In order to maintain the double-blind study, the administration of the IMP must occur individually and separately, and in the absence of the physician responsible for the study. This is because the reaction after its administration could be easily distinguishable between placebo and IMP.

10.3 Dose and Treatment Regimens in the Study

The IMPs will be administered orally once daily for 5 days (i.e., total of 5 administrations of IMP). On the morning of Day 1 to Day 5, each subject will receive a single oral dose of ATL-001 or placebo administered under fasting conditions as described above (Section 8.1). Subjects will fast overnight (at least 10 hours) prior to be dosed at approximately the same time on the morning of Day 1 through Day 5.

The first and last administration of the IMP (Day 1 and Day 5) will be performed at the hospital. At Day 2, prior to all clinical activities and assessments and to hospital discharge, the subject will be administered with the IMP. The other days (Day 3 to Day 4), treatment will be self-administered at home. During the first hospital admission (Day 1 to Day 2), subjects will be provided with the IMP to be administered daily from Day 3 to Day 4 and they will receive detailed instructions on how to properly take and storage the medication.

The starting dose in the Cohort 1 will be 0.2 mg/kg of ATL-001 or placebo. The doses in Cohort 2, Cohort 3, Cohort 4 and Cohort 5 are planned to be 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg of ATL-001 or placebo. These doses were selected based on pre-clinical data. Dose selection rationale is detailed in Section 6.3. ATL-001 dose to be administered from Day 1 to Day 5 should be calculated based on the subject’s weight assessed at Screening visit.

Upon consideration of all the available safety and tolerability data from all cohorts tested to date, the DSMB will provide recommendation for the progression to the next cohort or may recommend an

additional procedure to be taken (i.e., to test a different IMP dose or administration schedule), as outlined in Section 8.1.1.

10.4 Medical Care of Subjects after End of Study

Not applicable. The subjects in this study are healthy volunteers.

10.5 Blinding

To guarantee double-blind conditions, the IMPs will be presented in identical liquid syrups, and the subjects will take the same dosage of syrup on all treatment days. The sample labels had no information that would allow identification of the treatment administered.

The randomization schedule will be guarded by the Pharmacy Department during the development of the study experimental phase. A separate randomization list will be generated for each cohort of the study (Cohort 1, Cohort 2, Cohort 3, Cohort 4 and Cohort 5) to allow each cohort of the study to be unblinded independently. Individual randomization envelopes will be delivered by the responsible of generating random list to the site before the beginning of the trial. These will be kept unopened in a secure place accessible to the investigator team.

With the exception of the Sponsor unblinding team (CEO and Project Manager), Pharmacy department, unblinded nurse responsible of IMP administration, the randomization manager, the DSMB members where necessary, PK analysis responsible (see Section 11.2) and Quality Assurance (QA) auditors where necessary, all clinical and non-clinical staff including the data management staff assigned to the study at the clinical unit and the Sponsor will remain blinded to treatment allocation until after the database is locked for that part of the study. Cohort 1, Cohort 2, Cohort 3 and Cohort 4 may be unblinded separately after the respective database for that part of the study has been locked.

Whenever the maintenance of the safety and well-being of the subject, as assessed by the investigator, requires the knowledge of the actually administered IMP, the investigator shall break the blind. In addition, in the case of unintended pregnancy of subject or the female partner of a subject participating in the study the investigator could break the blind. In case of any doubt, the investigator should contact the Sponsor to evaluate whether or not the blind should be broken. The investigators will report about this event to the Sponsor as soon as possible. If unblinding occurs, the investigator must record the reason for unblinding, as well as the date and time of the event. Corresponding information will be recorded on the eCRF and will be documented in a note to file which will be filed in the trial master file (TMF). Randomization codes will be controlled in the IRT system and procedures for breaking the codes in an emergency will be made available to relevant members of study site staff. Unless required by an emergency, the disclosure of the randomization list will be done after database lock.

The designated pharmacovigilance personnel will obtain the subject's treatment identity information only when there is a Suspected Unexpected Serious Adverse Reaction (SUSAR).

10.6 Prior and Concomitant Therapy

Prior medications are defined as all medications taken within 8 weeks prior to the Screening Visit (whether continuing or not). The use of all medication taken by the subject must be recorded in the appropriate sections of the eCRF.

10.6.1 Permitted Medications

No concomitant medications will be allowed during the treatment period of the study.

If considered necessary for the subject safety and well-being, concomitant medication may be given at the discretion of the Investigator. However, concomitant medication administered during the study may lead to withdrawal of the subject from the study (see Section 9.4). Decisions regarding replacements of subjects requiring concomitant medications will be discussed with the Sponsor on a case by case basis.

10.6.2 Prohibited Medications

All concomitant medications will be forbidden during the treatment period of the study. Specifically, the following medications will be prohibited:

- Medications that interfere with the glucuronidation metabolic pathway
- Antineoplastic or anticancer drugs

10.7 Treatment Compliance

All IMP administrations will be daily recorded by the subject in the subject diary, ensuring treatment compliance for all subjects. The two firsts and last administrations of the IMP (Day 1 and Day 5) will be performed at the hospital.

If an administration is omitted for any reason, the continuation of the IMP or possible withdrawal of the subject will be discussed with Sponsor and decided on a case-by-case basis.

10.8 Drug Accountability

In accordance with GCP, the unblinded team member at each Investigational Sites will account for all supplies of the IMPs. Details of receipt, storage, assembly and return will be recorded. The precise amount of medication administered to each subject has to be documented in the subject's medical records, eCRF for each subject and study drug accountability records.

All unused supplies of the IMPs will either be destroyed or returned to the Sponsor at the end of the study in accordance with instruction by the Sponsor. If destroyed locally, a certificate of destruction must be provided to the Sponsor.

The unblinded team member should keep the used vials and only discard them after the Drug Accountability.

11. STUDY ASSESSMENTS

11.1 Efficacy Assessments

This is a Phase I study in healthy subjects. The efficacy of the IMP will not be tested.

11.2 Pharmacokinetic Assessments

Drug concentration information that may unblind the study will not be reported to the investigational site or blinded personnel until the study has been unblinded. Drug concentrations will, however, be disclosed to the PK analysis responsible person after completion of each cohort for PK model parameter estimation and simulation of plasma profiles of the subsequent cohort. The PK analysis responsible person will simulate plasma concentration profiles with variability of ATL-001 for the proposed dose of the next cohort. The timing of the plasma concentration reporting, the modelling and the simulation will be such that the DSMB meetings can be informed while the overall timelines of the study will not be jeopardized.

11.2.1 Sampling Procedures

Blood samples will be collected at specific time points throughout the study. The maximum amount of blood to be collected for PK analyses along the study is 5 mL in each extraction point. For each day when a PK sampling is collected a total amount 60 mL of blood (12 points) will be withdrawn.

The timing of the sampling is described in Section 8.2.1 and Table 1.

Details on collection, storage and handling of blood samples will be included in the respective Laboratory Manual.

11.2.2 Bioanalytical Method

The bioanalytical analysis will be performed by Covance Labcorp using approved bioanalytical methodology. Raw data will be archived in the Labcorp archives.

11.2.3 Definition and Calculation of Pharmacokinetic Parameters

The following PK parameters will be derived from each individual plasma concentration versus time profile using standard methods if the data warrant doing so (Table 11).

Table 11. Pharmacokinetic Parameters to be Analyzed

Parameter	Definition
C_{max}	Maximum observed plasma concentration
t_{max}	Time until C_{max} is reached
AUC $_{(0\text{-last})}$	AUC from time 0 to the time of the last measured concentration
AUC $_{(0\text{-}12)}$	AUC from time 0 to 12 hours after drug administration
AUC $_{(0\text{-}24)}$	AUC from time 0 to 24 hours after drug administration
$t_{1/2}$	Plasma concentration half-life
CL/F	Apparent total body clearance
Vz/F	Apparent volume of distribution

11.3 Demographic and Other Baseline Characteristics

11.3.1 Demographic and Baseline Data

The following demographic and baseline data will be collected at the Screening Visit:

- Age
- Sex
- Race
- Weight (for dose calculation from Day 1 to 5)
- Height
- BMI – calculated

11.3.2 Medical History

Past (within 6 months prior to screening visit) or current medical conditions judged relevant by the investigator including general, head and neck, eyes, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse or any other diseases or disorders.

The timing of the sampling is described in Section 8.2.1 and Table 1.

11.3.3 Prior and Concomitant Medication

Prior medications taken within 8 weeks prior to screening will be recorded at the Screening visit.

Concomitant medication will be recorded on the concomitant medication log/page of the eCRF throughout the study.

11.4 Safety Assessments

11.4.1 Safety Variables

The following safety variables will be measured:

- AEs
- Physical examination
- Vital signs
- ECG
- Laboratory safety assessments (including viral serology and drugs of abuse, and alcohol screen)

11.4.2 Adverse Events

AEs will be recorded during the study period from the informed consent signatory to the completion of the FU-V2 (30 days after the last IMP dose). For further information of definitions and reporting of AEs and SAEs, see Section 12 below.

11.4.3 Physical Examination

All subjects will undergo a standard physical examination. General physical examinations will include the following body systems: heart, lung, abdomen, nervous system, skin, musculoskeletal system, lymph nodes, limbs, head, ears, eyes, nose, throat, and others.

The examinations will be recorded and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”.

The timing of the assessments is described in Section 8.2.1 and Table 1.

11.4.4 Vital Signs

The following vital signs will be monitored as safety variables:

- Resting systolic and diastolic blood pressure (mmHg), after 5 minutes sitting
- Resting pulse rate (beats per minute), after 5 minutes sitting
- Axillary body temperature (°C)

Additional vital signs may be monitored for the safety of the subjects.

The observed values will be recorded and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”.

The Investigator may choose to repeat any abnormal result once, in order to rule out measurement error. Clinically relevant deviations of vital signs results occurring during or at post- study examination must be reported and discussed with the Sponsor, if applicable. Repeated measurements are mandatory until their normalization or until the time course and reason of the underlying process can clearly be assessed positively.

The timing of the assessments is described in Section 8.2.1 and Table 1.

11.4.5 Electrocardiogram

A standard 12-lead ECG will be performed by authorized site staff after the subject has been calmly resting in a supine position for a minimum of 5 minutes before obtaining the ECG. ECGs should precede measurement of vital signs and blood draw for clinical laboratory tests.

ECG findings will be recorded and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”.

The timing of the assessments is described in Section 8.2.1 and Table 1.

11.4.6 Laboratory Safety Assessments

The laboratory safety analyses (hematology, biochemistry, urinalysis, viral serology and drugs of abuse, and alcohol test) will be performed by the local laboratory at site. The following laboratory safety parameters will be measured (Table 12):

Table 12. Laboratory Safety Parameters

Category	Laboratory Parameter	Units		
		Conventional	SI	Site Laboratory
Biochemistry	Alkaline phosphatase	U/L	µkat/L	IU/L
	Alanine aminotransferase (SGPT)	U/L	µkat/L	IU/L
	Aspartate aminotransferase (SGOT)	U/L	µkat/L	IU/L
	Calcium	mg/dL	mmol/L	mg/dL
	Chloride	mEq/L	mmol/L	mmol/L
	Creatinine	mg/dL	µmol/L	mg/dL
	Gamma glutamyl transferase (GGT)	U/L	µkat/L	IU/L
	Glucose	mg/dL	mmol/L	mg/dL
	Lactate dehydrogenase (LDH)	U/L	µkat/L	IU/L
	Potassium	mEq/L	mmol/L	mEq/L
	Sodium	mEq/L	mmol/L	mmol/L
	Bilirubin; Total Bilirubin	mg/dL	µmol/L	mg/dL
	Triglycerides	mg/dL	mmol/L	mg/dL

Category	Laboratory Parameter	Units		
		Conventional	SI	Site Laboratory
	Urea	mIU/L	mIU/L	uIU/mL
	Thyroid stimulating hormone (TSH) Thyrotropin	mIU/L	IU/L	mIU/mL
	Follicle stimulating hormone (<2 years post-menopausal females only) (FSH)	mL/min	mL/min	mL/min
	eGFR (only at Screening)			
Hematology	C reactive protein (CRP)	mg/L	nmol/L	mg/L
	Ferritin	ng/mL	pmol/L	ng/mL
	Hemoglobin	g/dL	g/L	g/dL
	Erythrocytes; Red Blood Cells	$\times 10^6$/µL	$\times 10^{12}$/L	$\times 10^6$/µL
	Leukocytes; White Blood Cells	/µL	$\times 10^9$/L	$\times 10^3$/µL
	Basophils	/µL	$\times 10^9$/L	$\times 10^3$/µL
	Eosinophils	/µL	$\times 10^9$/L	$\times 10^3$/µL
	Lymphocytes	/µL	$\times 10^9$/L	$\times 10^3$/µL
	Monocytes	/µL	$\times 10^9$/L	$\times 10^3$/µL
	Neutrophils	/µL	$\times 10^9$/L	$\times 10^3$/µL
Urinalysis	Color	-	-	-
	Specimen Appearance	-	-	-
	pH	-	-	-
	specific gravity	g/mL	kg/m3	Ratio
	Bilirubin; total bilirubin	Neg./Pos.	Neg./Pos.	Neg./Pos.
	Glucose	Neg./Pos.	Neg./Pos.	Neg./Pos.
	Ketones	Neg./Pos.	Neg./Pos.	Neg./Pos.
	Nitrite	Neg./Pos.	Neg./Pos.	Neg./Pos.
	Occult blood	-	-	Neg./Pos.
	Erythrocytes; Red Blood Cells	RBC/µL	-	/HPF
	Leukocytes; White Blood Cells	WBC/µL	-	/HPF
	Albumin	mg/L	g/L	mg/dL
	Total Protein	mg/L	g/L	mg/dL
	Uric acid crystals	Neg./Pos.	Neg./Pos.	Neg./Pos.
Drugs of abuse and alcohol parameters*	Amphetamine	-	-	-
	Barbiturates	-	-	-
	Benzodiazepine	-	-	-
	Ethanol	-	-	-
	Cocaine	-	-	-
	Opiate	-	-	-
	Phencyclidine	-	-	-
	Cannabinoids	-	-	-
	Cotinine	-	-	-
Viral Serology*	Hepatitis B Virus Surface Antigen (HBsAg)	-	-	-
	Hepatitis C Virus (HCV) Antibody	-	-	-
		-	-	-

Category	Laboratory Parameter	Units		
		Conventional	SI	Site Laboratory
	Human Immunodeficiency Virus (HIV) antibody I and II COVID-19			

*Only at Screening and/or Baseline (Day 1).

The observed values will be recorded in the eCRF and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”.

Blood and urine samples will be collected at specific time points throughout the study. The timing of the assessments is described in Section 8.2.1 and and Table 1.

Details on collection, storage and handling of blood and urine samples will be provided in the respective Laboratory Manual.

Blood and Urine Volumes

The maximum amount of blood and urine to be collected for laboratory safety assessments (hematology, biochemistry, and urinalysis) along the study are 50 mL and 50 mL, respectively. For each day when a laboratory safety assessment sampling is collected, 5 mL of blood and 5 mL of urine will be withdrawn.

11.5 Appropriateness of Measurements

Standardized methods for measurements of safety and PK variables will be used.

12. ADVERSE EVENTS

AEs will be daily recorded by the subject in the subject diary. All AEs will be reported and documented as stated below. The investigator will instruct study subjects on how to complete the subject diary.

The Investigator is responsible for appropriate medical care of the subjects during the study.

The Investigator remains responsible for following through an appropriate healthcare option with study subjects who experienced AEs that are serious or that caused the subject to discontinue before completing the study.

12.1 Definitions

12.1.1 Adverse Event

Adverse events and grading criteria will be defined based on Common Terminology for Adverse Events (NCI – CTCAE), following the most updated version from National Cancer Institute (v. 5.0 or higher when available).

Any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Medical disorders present at the time of signing the informed consent are only considered AEs if they worsen after this time. All baseline conditions should be recorded as part of Medical History.

All AEs occurring after the initiation of the treatment are referred to as treatment-emergent AEs (TEAEs). All AEs occurring prior to the initiation of the treatment will be referred to as non-TEAEs, which include any unintended sign, symptom, or disease that occurs between the screening and the first IMP administration of the clinical study. A TEAE also includes an AE present prior to administration of IMP which worsened after administration of IMP.

12.1.2 Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

12.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorized IMP or summary of product characteristics for an authorized product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

12.1.4 Serious Adverse Event

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

"Life-threatening" in the definition of a SAE or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgement should be exercised in deciding whether an AE/reaction is serious in other situations. Important AEs/reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

12.1.5 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is an AE that is assessed as serious, related and unexpected.

12.2 Reporting of Adverse Events

All study subjects will be carefully monitored for the occurrence of AEs during the study period from the informed consent signatory to the completion of the follow-up visit (30 days after the last IMP dose). AEs will be daily recorded by the subject in the subject diary.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the subject, or reported in answer to an open question by the Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding study drug
- Opinion on causality
- Seriousness
- Outcome

Severity

Severity describes the intensity of an event, and will be assessed as:

Mild

The AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.

Moderate

The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe

The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the subject.

If an AE changes in severity, the worst severity should be reported.

Causality

Causality will be assessed as:

Related to the Study Treatment

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study treatment administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study treatment (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probable: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study treatment, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study treatment). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Not Related to the Study Treatment

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study treatment administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study treatment) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Not Related: The AE is completely independent of study treatment administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Follow-up of Subjects after Adverse Events

Any AE that is ongoing when the subject is withdrawn from the study should be followed up until the AE is resolved or the Investigator decides that the AE is stable and needs no further follow-up. The date when the Investigator considers one of these outcomes to have occurred for the last ongoing AE for a subject will be considered the last visit for this subject, and the outcome should be recorded in the eCRF.

Abnormal Laboratory Values/Vital Signs

The reporting of abnormalities as both laboratory/vital signs findings and AEs should be avoided.

An asymptomatic abnormal laboratory/vital sign finding should only be reported as an AE if it is clinically significant, if it fulfils the criteria for a SAE or if it causes the subject to discontinue the study.

If an abnormal laboratory/vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory/vital sign result should be considered additional information.

12.3 Reporting of Serious Adverse Events

The Investigator is responsible for ensuring that all SAEs are reported to the Sponsor immediately, but in any event no later than 24 hours of any site staff becoming aware of the event. Initial reports should be followed as soon as possible by detailed written reports. The initial and follow-up reports should identify subjects by unique code numbers assigned in the study. The subjects' names, personal identification numbers, and/or addresses must not be included. The following information is **mandatory** for the initial report:

- Subject study ID
- Study treatment (blinded, if applicable)
- Start date (time, if relevant) of the study treatment

- Brief description of the event (diagnosis)
- Start date (time, if relevant) of the event
- Seriousness criteria
- Causality assessment

For reported deaths, the Investigator should supply the Sponsor and the IRB (if applicable) with any additional requested information (e.g., autopsy reports and terminal medical reports).

For reporting of severity, causality, follow-up of subjects after SAEs and SAE reporting in conjunction with abnormal laboratory values/vital signs see Section 12.2.

SAE REPORTING CONTACT DETAILS

Name: Pivotal, S.L.U.

E-mail: drugsafety@pivotalcr.com

12.4 Reporting of Suspected Unexpected Serious Adverse Reactions

The Sponsor is responsible for informing the RA and IRB of any individual case reports of SAEs that are determined to be reportable by the Sponsor (i.e., SUSARs) in accordance with US legislation. The Investigator will ensure that all relevant information is provided to the Sponsor to allow the Sponsor to meet their obligations to report the SUSAR to the RA and IRB. For a SUSAR that is fatal or life-threatening, this should be reported as soon as possible and not later than 7 days after the Sponsor was first advised, for any other SUSAR this should be within 15 days.

12.5 Adverse Events of Special Interest

AEs of special interest (AESIs) include all gastrointestinal events which have been assessed as related to the study treatment.

12.6 Precautions/Overdose

Considering that the main aim of this Phase I clinical trial is to investigate the safety and tolerability of multiple and increasing doses of ATL-001, the dose which is considered an overdose has not been determined. However, if a subject receives a dose exceeding 100 mL of ATL-001, this will be considered an overdose, and in such case, the information will be collected following the same timeframe and procedures as for a SAE, even if the overdose is not associated to any AE/SAE. No specific treatment is recommended apart from appropriate supportive measures.

12.7 Pregnancy

Female subjects will be instructed to notify the Investigator immediately if they become pregnant during the study. Male subjects will be instructed to notify the Investigator immediately if their partner becomes pregnant. Pregnant subjects will be withdrawn from further study treatment. The subjects will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the study.

A pregnancy as such is not an AE, unless there is a possibility that the IMP has interfered with the efficiency of any contraceptive measures. However, the Investigator should report pregnancies according to the procedures and timelines described for reporting of SAEs (Section 12.3). The pregnancy report form should be used instead of the SAE form.

The pregnant subject or partner will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE or SAE (if it fulfils SAE criteria). The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as a SAE.

13. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

13.1 Statistical and Analytical Plans

A separate statistical analysis plan (SAP), which will provide more details of the statistical analysis outlined below, will be prepared and approved prior to unblinding the study data. No formal statistical hypothesis of the safety or tolerability are to be tested for this study.

13.1.1 Data Sets to be Analyzed

The analysis sets are defined as follows:

- **Safety set:** All randomized subjects who receive at least one dose of the study medication regardless of if they have or have not completed the study.
- **PK set:** All randomized subjects who received at least one dose of the study drug medication and have at least one valid PK measurement.

The analysis of safety and tolerability will be based on the Safety set. PK analysis will be based on the PK set.

Definitions

Baseline is defined as the last non-missing measurement before first treatment administration on Day 1.

13.1.2 Statistical Issues

13.1.2.1 Level of Significance, Multiple Comparisons and Multiplicity

Results of statistical analysis will be interpreted descriptively by treatment arm. All statistical models applied will foremost be used as tools for exploring treatment differences between treatment arms rather than formal testing of hypotheses. For this reason, corrections for multiple testing will not be applied in this study and, therefore, confidence intervals (CIs) or p-values indicating statistically significant differences between treatments should be interpreted as suggestive rather than evidence of differences.

13.1.2.2 Adjustment for Covariates

No adjustment for covariates is planned for this study.

13.1.2.3 Handling of Dropouts and Missing Data

No missing value imputation will be done. All analyses will be conducted on observed data.

13.1.3 Summary Statistics

In general, data will be summarized by means of summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, first quartile (Q1), median, third quartile (Q3) and maximum value. Categorical data will be presented as counts and percentages. The data will be presented for each treatment group by visit.

Individual subject data will be listed.

13.1.4 Primary Endpoint Analysis

The primary safety endpoint will be analyzed in the Safety set.

13.1.4.1 Safety

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs and AESIs will be summarized and presented by treatment group.

The total number of subjects with at least 1 AE and the total number of AEs will be presented.

The number of subjects and the number of AEs will be tabulated by SOC and by preferred term. AEs will also be tabulated versus worst severity and worst relationship to study medication. In summaries of severity and relationship, subjects who report more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship, accordingly.

SAEs will be separately tabulated and listed. The number of AEs leading to discontinuation will also be tabulated.

13.1.4.2 Tolerability

Descriptive statistics will be calculated for the quantitative variables obtained in the vital signs records, ECG, physical examination and laboratory safety tests (hematology, biochemistry and urinalysis).

Vital Signs

Vital signs data will be presented by individual listings with flagging of abnormal values. Vitals signs data will be summarized by visit and treatment group, together with changes from baseline.

Electrocardiogram

Overall interpretation of ECG results (i.e., normal or abnormal) will be summarized. In addition, standard ECG parameters will be summarized by treatment group, together with changes from baseline.

Physical Examination

Physical examination data will be summarized by treatment group.

All abnormal physical findings will be listed.

Laboratory Safety Assessments

For laboratory data (hematology, biochemistry, and urinalysis), summary statistics will be produced for observed values and for changes from baseline to each visit. In addition, the number of abnormal and clinically significant observations will be tabulated for each treatment group by visit. Abnormal values will be flagged in listings.

Shift tables will be created for a subset of laboratory parameters, which will be defined in the SAP. Shift tables will show the number of subjects who changed from below, within or above the reference range at baseline to below, within or above the reference range at each time of assessment.

For laboratory values which are below the limit of quantification, the value corresponding to the limit of quantification will be used when summarizing data.

13.1.5 Secondary Endpoint Analyses

The secondary PK endpoint analysis will be conducted on the PK set.

13.1.5.1 Pharmacokinetic Analysis

ATL-001 plasma concentration data will be listed by treatment, subject and visit/sampling time point. Descriptive summary statistics will be provided by treatment, and visit/sampling time point, including the frequency (n, %) of concentrations below the limit of quantification and reported as zero.

Summary statistics will include mean (arithmetic and geometric), standard deviation, coefficient of variation (arithmetic and geometric), median, minimum, and maximum. An exception to this is t_{max} where median, minimum and maximum will be presented. Concentrations below limit of quantification will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the data set includes zero values. The PK data of all subjects who received at least one dose of ATL-001 and who have at least one valid PK measurement will be used in the PK set analysis.

A non-compartmental analysis will be used to calculate the PK parameters detailed on Section 11.2. A normalization by dose will be performed in the main PK parameters ($AUC_{(0-t)}$ and C_{max}).

Unassessable subjects for the PK analysis are:

- Subjects who experienced an AE (e.g., vomiting) and took (or not) concomitant medication, if the experienced AE itself and/or the concomitant medication taken, interferes in a relevant manner with his PK results
- Subjects missing more than four samples throughout the study period.
- Excessive deviation between consecutive blood samples collection from scheduled time of sample collection (more than 10% of the time period between consecutive samplings)
- Subjects with lack of any measurable concentration or only very low plasma concentration for drug product*
- Subjects with non-zero baseline concentration > 5% of C_{max}*
- Subjects with less than three quantifiable concentrations*

*Except for these criteria, decision to exclude a subject from the statistical or PK analysis must be made before bioanalysis and has to be properly documented.

More details on the PK parameters, analysis and presentation of study results will be provided in the PK analyses SAP.

13.1.6 Demographic and Other Baseline Characteristics

Subject disposition, demographic and other baseline data will be presented using summary statistics. The Safety set will be used for this presentation.

13.1.7 Exposure to Treatment

The number of IMP administrations will be summarized. Compliance will be calculated as the percentage of actual doses the subject took with respect to the total doses planned. The Safety set will be used for this presentation.

13.1.8 Concomitant Treatment

Concomitant medication and concomitant therapy will be summarized as number of subjects being treated with each type of medication/therapy classified according to ATC level 3 and World Health Organization (WHO) Drug Dictionary preferred term. The Safety set will be used for this presentation.

13.2 Determination of Sample Size

The study will consist of five sequentially recruited cohorts of 8 subjects each, resulting in up to 40 randomized subjects.

No technical sample size calculation was done.

This sample size of 8 subjects per cohort with a randomization 3:1 for active/placebo treatment, is regarded sufficient to demonstrate the effects of the study drug under investigation and therefore to be sufficient to fulfill the objectives of the study.

In case of a withdrawn subject from the study during the treatment period and for other reasons than safety, he/she may be replaced with another subject, at the Sponsor's discretion. All subjects receiving at least one dose of the study medication will be evaluated for safety.

13.3 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Any deviation(s) from the original SAP (as described in the study protocol or in the SAP) will be described and justified in a protocol amendment and/or in a revised SAP and/or in the final report, as appropriate.

13.4 Interim Analysis

The safety and tolerability data will be reviewed for each cohort during the DSMB meetings (see Section 8.1).

In addition, a Statistical Analysis has been conducted after completing Cohort 4 (2 mg/kg) and before enrolling subjects in Cohort 5 (4 mg/kg).

14. RESULTS FROM THE ANALYSIS REGARDING SAFETY AND EFFICACY OF COHORTS 1 TO 4 ARE AVAILABLE IN SECTION 6.3 OF THE IB.INVESTIGATOR/SPONSOR RESPONSIBILITIES

14.1 Ethics and Regulatory Aspects

14.1.1 Institutional Review Board and Regulatory Authority (if applicable)

This protocol, proposed Informed Consent Form and other information provided to subjects, and all appropriate amendments will be submitted to the applicable IRB and RA, for review and approval. This study will be conducted only after approval of the protocol has been granted by the appropriate IRB and a copy of the approval has been received by the Sponsor

The investigator must not screen any subjects before receiving written approval from the IRB.

The investigator will provide required progress reports and report all SAEs to the IRB as required by the IRB.

14.1.2 Ethical Conduct of the Study

The study will be conducted in compliance with the protocol, US CFR applicable to clinical studies (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312), GCP and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

14.1.3 Subject Information and Consent

In obtaining and documenting informed consent, the investigator must comply with 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and should adhere to International Conference on Harmonization (ICH) GCP.

All subjects will receive written and verbal information regarding the study at a prior interview. This information will emphasize that participation in the study is voluntary and that the subject may withdraw from the study at any time and for any reason. All subjects will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study.

It is the personal responsibility of the investigator to obtain written informed consent from the subject and/or his/her legal representative (if applicable). No study-related procedures, including any screening procedures, may be performed before the investigator has obtained written informed consent from the subject and/or his/her legal representative.

Prior to obtaining written informed consent, the investigator or a designee must explain to potential subjects and/or their legal representatives, the aims, methods, and potential hazards of the study and any discomfort it may entail.

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the subjects and/or their legal representatives. Prior to enrolling a subject in the study, an Informed Consent Form must be signed and dated by the subject and/or his or her legal representative and the investigator on the same day. The subjects and/or their legal representatives will receive a copy of the written information (Subject Information Sheet) as well as a copy of the signed Informed Consent Form.

If parts of the informed consent process (such as giving information) may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

The investigator must identify vulnerable subjects, that is, subjects whose willingness to participate in a clinical study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Subjects thus identified must be excluded from participation in the study.

The data will be processed in accordance with the specifications outlined by the federal or state law to ensure that requirements regarding personal data protection are met (e.g., Health Insurance Portability and Accountability Act rules). If an external organization will process data on behalf of the Sponsor, a contractual procedure will be signed between the Sponsor and the external organization to ensure compliance with the above-mentioned legislation.

Additionally, in case the partner of a participant subject become pregnant, she will receive written and verbal information regarding the study and her participation in the pregnancy follow-up. This information will emphasize that participation in the follow-up is voluntary and that the subject may withdraw from the follow-up at any time and for any reason.

All subjects will be given the opportunity to ask questions about the research and will be given sufficient time to decide whether to participate.

14.2 Subject Records and Source Data

The origin of source data in the study will be further specified in a separate document ("Origin of Source Data").

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the subject is in a clinical study
- The identity of the study e.g., Study code
- Subject screening number and/or subject number
- That informed consent was obtained and the date
- Dates of all visits during the study period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of study termination
- Subject health service identification number

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRF. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The Sponsor should ensure that the investigator has control of and continuous access to the eCRF data reported to the Sponsor. The Sponsor should not have exclusive control of those data.

If due to COVID-19 pandemic situation, whereby on-site visits are not allowed by site or government policies, remote source data verification (rSDV) may be implemented, if allowed/approved by required authorities. In order to ensure subject´s safety and/or validity of key study data the monitor may receive remote access to source documents via a secure remote viewing solution/secure electronic system or repository that meets all data protection requirements and regulatory requirements of the country where the study site is located. Following data may be reviewed remotely:

- Informed Consents
- Important safety data
- Important PK data

14.3 Data Protection

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject initials, demographics (including birthdate), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study subjects. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (i.e., aggregate) form, and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study.

14.3.1 Purpose of Processing

The processing of personal data of subjects taking part in the study must be for the sole purpose of carrying out scientific research of public interest. This includes the management of data relating to subjects suitable for research, in order to allow the collection, entry, validity and consistency check and analysis of the data collected during the research.

14.3.2 Origin and Nature of the Data

Need for the Use of Personal Data

The identification of persons suitable for research may only be carried out in databases containing personal health data established for the conduct of research, by means of a serial number or an alphanumeric excluding any directly identifying personal data.

Only professionals and their collaborators involved in research in a research location can keep the link between the coded identity of people participating in the research used to associate personal health data and their name (s) and first name (s) (correspondence table kept securely).

Origin of Personal Data

Data relating to persons suitable for research must come exclusively:

- from the interested parties themselves and / or their legal representative(s)
- professionals involved in research
- databases and / or collections of biological samples, legally constituted and having undergone the necessary formalities with the RAs.

Nature/Categories of Personal Data

The Sponsor undertakes to collect only the data that is strictly necessary and relevant with regard to the research objectives. Consequently, each of the categories of data can only be collected if their processing is scientifically justified in the research protocol.

14.3.3 Recipients of Processed Personal Data

Under the responsibility of the Sponsor or in application of specific legal or regulatory provisions, the categories of persons described below have access to the data processed, within the limits of their powers, with regard to their functions and under conditions in accordance with US regulations. Data will only be transferred to countries or organizations where an adequate level of data protection has been established. These categories of people are subject to confidentiality obligations.

Recipients of Indirectly Identifying Data

The following may be recipients of indirectly identifying data concerning the subjects participating in the research:

- the Sponsor and the natural or legal persons acting on its behalf
- the investigator
- professionals involved in research and personnel acting under their responsibility or their authority

- the staff of group companies to which the data controller belongs and whose participation is necessary for the processing of data in the context of research
- the persons responsible for the collection, quality control, processing, and analysis of the data
- staff of health authorities and public control authorities legally empowered, within the framework of a specific mission or the exercise of a right of communication

Recipients of Directly Identifying Data

The following may be recipients of directly identifying data concerning the persons participating in the research:

- professionals involved in research and personnel acting under their responsibility or their authority, concerning the persons for whom they provide care in the context of research
- the persons responsible for quality control and assurance, during visits, audits or controls within the investigation sites, responsible for controlling and evaluating the quality and authenticity of the data collected, and in particular by comparing the data recorded with the content of source documents. These persons also ensure, under the responsibility of the controller, that the provisions relating to the integrity and protection of individuals are respected.

14.4 Access to Source Data and Documentation

The Investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate RAs, and the IRB, if required.

14.5 Monitoring

The monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use are described in detail in the risk-based monitoring plan (RBMP).

Centralized monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to perform monitoring activities that cannot be performed remotely.

The monitor will visit the study site on a regular basis (whenever possible) to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any study specific documents such as eCRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol
- Informed consent has been obtained from all subjects
- AEs have been reported as required
- Data are being accurately recorded in the eCRFs
- IMP is being stored correctly and drug accountability is being performed on an on-going basis
- Facilities are, and remain, acceptable throughout the study
- The Investigator and the site are receiving sufficient information and support throughout the study

Moreover, during monitoring visits the data recorded in the eCRFs, source documents and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the subject in the study i.e., source data verification.

In the exceptional event of a lockdown or limitation of the people's mobility due to the COVID-19 pandemic, rSDV may be used optionally to ensure subject safety and data integrity. rSDV would be:

- Conducted after an internal risk-assessment was completed
- Limited to the safety and tolerability data

- Conducted only after the subject's consent was obtained. Where written consent cannot be obtained (as a result of COVID-19), verbal consent will be obtained, and the subject will be asked to send an email confirming their consent
- Conducted in agreement with the institution/ primary investigator and the institution's Data protection officer
- Conducted after site staff is appropriately trained
- Conducted by reviewing pseudonymized copies of source documents
- Study subject records will be viewed remotely via a web-based platform that complies with national, local and industry-specific regulations.

Details of rSDV:

- The device through which the subject's medical records are accessed will have adequate security, such as adequate firewalls, secure log-in and passwords and will not be left unattended and accessible.
- To maintain confidentiality, the trial monitor will ensure that when accessing subject records that they cannot be viewed or accessed by anyone who is not part of the study team.
- In addition, any of the information remotely viewed by the monitor will not be retained, printed, emailed or downloaded by the monitor.
- All subject records will be released for review by clinical trial site staff. They will have complete control over records made available remotely to the monitor.

14.6 Data and Safety Monitoring Board

During the study, a DSMB will periodically review safety data from study subjects and will make recommendations concerning the continuation, modification or termination of the trial (see Section 8.1.1).

A DSMB charter document, which describes the composition and details the roles and responsibilities of the DSMB will be prepared for the study. It will also outline what data will be provided to the DSMB, the process for disseminating study data, and the communication plan.

14.7 Data Management

Data management and handling of data will be conducted according to the study specific Data Management Plan with ICH guidelines and Atlas Molecular Pharma S.L. standard operating procedures (SOPs).

A 21 CFR Part 11-complaint eCRF system will be used to capture data from the study. Data entry will be performed by the study site personnel. Validation and data queries will be handled by the Atlas Molecular Pharma S.L. Data Management Team. The data will be subjected to validation according to Atlas Molecular Pharma S.L. SOPs in order to ensure accuracy in the collected eCRF data.

Changes to the data in the eCRF will be made at the site by the study site personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to lock the data and identify the person entering or changing the data.

Before database closure a reconciliation will be performed between the SAEs entered in the safety database and the study database. After database closure, the database will be exported as SAS® data sets.

Any deviations, i.e., discrepancies and additions from the process initially described in the Data Management Plan, will be described in the following updates of the Data Management Plan or at the end of the study in a study specific Data Management Report.

14.8 Quality Management

The quality management approach implemented is described in detail in the RBMP.

14.9 Quality Assurance and Audit

Audits or inspections, including source data verification, may be performed by representatives of the Sponsor, a RA and/or an IRB.

14.10 Record Retention

The Investigator/institution should maintain essential documents (as defined in ICH E6 (R2) GCP, Section 8) as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of the documents.

Essential documents should be retained according to applicable regulatory requirements of the country(ies) where the product is approved, and/or where the Sponsor intends to apply for approval.

It is the responsibility of the Sponsor to inform the Investigator/institution in writing as to when the documents no longer need to be retained.

14.11 Protocol Deviations

A protocol deviation is any noncompliance with the protocol or GCP requirements. The classification of protocol deviations in major or minor deviations will be mutually agreed between the Sponsor and the responsible contract research organization (CRO) at the start of the study.

A major protocol deviation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting entry criteria, administration of study treatment, administration of prohibited medication or withdrawal criteria.

Failure to comply with GCP guidelines will also result in a major protocol deviation. The Sponsor will determine if a major protocol deviation will result in withdrawal of a subject.

Deviations to the study protocol will be documented in a Protocol Deviation Log.

The Sponsor or delegate is responsible for immediately reporting serious breaches according to applicable regulations, as well as deviations from the study protocol that substantially affect the integrity or the safety of the subjects or the scientific validity of the study, to the RA/IRB.

Protocol deviations will be reviewed during a meeting before database lock in order to allocate the subjects into the different analysis sets.

14.12 Insurance

The Sponsor must provide insurance or must indemnify (legal and financial coverage) the Investigator/the institution against claims arising from the study, except for claims that arise from malpractice, negligence or non-compliance with the protocol.

14.13 Report and Publication

The Sponsor or its delegate will post the clinical study information and summary of results on www.clinicaltrials.gov, in accordance with applicable regulations.

After completion of the study, a clinical study report will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3) by the Sponsor designee in close collaboration with the Investigator and the Sponsor. The Sponsor or its delegate will post results from this clinical study on external/national registries, as required by law.

Upon study completion and finalization of the study report, the results of this trial may be submitted for publication (e.g., peer-reviewed journal). All publications and presentations must be based upon the clinical study report. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. The list of authors of any publication of study results may include representatives of the Sponsor and will be determined by mutual agreement.

The presentation of the results of data processing cannot in any case allow the direct or indirect identification of persons who participated to the clinical study.

All information supplied by the Sponsor in connection with this study will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be

disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this study.

If an investigator wishes to publish results from this clinical study, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the IMP and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript prior to their submission to journals, meetings or conferences.

The Sponsor may choose to publish or present data from this study. If an Investigator is offered authorship, he/she will be asked to critically review the article for important intellectual content and approve the version to be published. The Sponsor has the right to use the results for registration and internal presentation and for promotion of the Sponsor's commercial interests.

15. REFERENCE LIST

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7. Minden MD, Hogge DE, Weir SJ, Kasper J, Webster DA, Patton L, et al. Oral ciclopirox olamine displays biological activity in a phase I study in patients with advanced hematologic malignancies. Am J Hematol. 2014 Apr;89(4):363–8.

16. CLINICAL STUDY PROTOCOL AGREEMENT FORM

I have read the clinical study protocol entitled "A Phase I, double-blind, randomized, placebo-controlled study to assess the safety and pharmacokinetics of ATL-001 (ciclopirox olamine) in healthy volunteers" and verified that it contains all necessary information for conducting the study.

I hereby confirm that:

- I have carefully read and understood this clinical study protocol
- my staff and I will conduct the study according to the study protocol and will comply with its requirements, including ethical and safety considerations
- my staff and I will conduct the study in accordance with ICH GCP – E6 (R2) and in accordance with the Declaration of Helsinki and local regulations

I understand that, should the Sponsor decide to prematurely terminate or suspend the study for whatever reason, such decision will be communicated to me in writing. Conversely, if I decide to withdraw from execution of the study, I will immediately communicate such a decision to the Sponsor.

I agree not to publish any part of the results of the study carried out under this clinical study protocol without consulting the Sponsor.

Principal Investigator: _____

Date: _____

Signature: _____