Clinical Trial Protocol	
EudraCT No.	2021-006014-36
Investigational Medicinal Product	C106
Sponsor trial code	VP-C106-101
Protocol Version and Date	Final v4.0; 27FEB2023

A double-blind, placebo-controlled, within-group randomised, first-in-human, single-centre trial to evaluate the safety, tolerability and pharmacokinetics of single and multiple ascending oral doses of C106 in healthy male and female subjects

Phase	1, First-In-Human (FIH)
Indication	N/A
Test product	C106
Comparator product	Placebo (inactive control)
Sponsor signatories	[redacted]
Principal Investigator	[redacted]
Clinical trial conduct and management	CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance 85, 2nd level SE-751 85 Uppsala, Sweden

The following amendments have been made to the first regulatory approved version of this Clinical Trial Protocol (version 2.0).

Table 4.1-1 Changes to the clinical trial protocol

Type of change	Summary of changes	Revised protocol version
Substantial amendment	The proposed doses for the remaining planned SAD cohorts are 240 mg and 300 mg. The maximum daily dose of C106 is changed from 200 mg (100 mg BID) to 480 mg (240 mg BID). One (1) cohort is added to the MAD part (cohort B:4). The pre-dose ECG recordings will be done on Day 1 instead of Day- 1. ECG recordings and vital signs assessments will be done 40 minutes post-dose instead of 1-hour post-dose in order to perform the assessments closer to the assumed C_{max} timepoint, as recommended by the iSRC. Risk-assessments regarding COVID-19 has been updated according to current recommendations.	Version 2.0
Substantial amendment	An exploratory, non-invasive pharmacodynamic (PD) assessment of endothelial function will be performed using EndoPAT in Part B, cohort B:4 before the first IMP administration (Day -1 or Day 1) and 30±10 minutes after IMP administration on Day 7. The Sponsor address has been updated. The planned trial period has been extended until Q3 2023.	Version 3.0

1 TRIAL SYNOPSIS

Trial title A double-blind, placebo-controlled, within-group randomised, first-in-human, single-centre trial to evaluate the safety, tolerability, and pharmacokinetics of single and multiple ascending oral doses of C106 in healthy male and female subjects.	
Trial code VP-C106-101	**EudraCT No** 2021-006014-36
Planned trial period Q2 2022 to Q3 2023	**Phase of development** 1, first-in-human (FIH)
Principal Investigator Helena Litorp, MD, PhD CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance 85, 2nd level SE-751 85 Uppsala, Sweden	
Trial design This is a FIH, double-blind, placebo-controlled, within-group randomised, trial designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending oral doses of compound 106 (C106) in healthy females of non-childbearing potential and healthy males. The trial will be conducted in 2 parts: Part A, single ascending dose (SAD) including a food interaction cohort: safety, tolerability, and PK in healthy males and healthy females of non-childbearing potential receiving single ascending doses of C106. Part B, multiple ascending dose (MAD): safety, tolerability, and PK in healthy males and healthy females of non-childbearing potential receiving twice daily multiple ascending doses of C106 for 8 days.	
Objectives **Primary objective** To evaluate the safety and tolerability of single and multiple oral doses of C106 in healthy subjects. **Secondary objectives** • To characterise the PK of single and multiple oral doses of C106 in plasma and urine of healthy subjects. • To evaluate the effect of a high fat meal on PK after a single oral dose of C106 in healthy subjects (Part A). **Exploratory objectives** • To evaluate the metabolite profile of C106 in plasma of healthy subjects at steady state (Part B) • To estimate the excreted C106 and its metabolites, and the metabolite profile of C106 in urine of healthy subjects at steady state (Part B).	

- To collect and store electrocardiogram (ECG) data for potential future evaluation of the effect of C106 on ECG parameters, including concentration-QTc analysis using Expert Precision QT (EPQT) assessment (Part A)
- To evaluate the pharmacodynamic (PD) effect of C106 on endothelial function in healthy subjects at steady state (Part B, cohort B4).

Endpoints

Primary endpoints

- Treatment Emergent adverse events (AEs) and serious AEs (SAEs).
- Clinically relevant changes in:
  - 12-lead electrocardiograms (ECGs).
  - Vital signs (blood pressure, heart rate (HR), body temperature and respiratory rate
  - Laboratory safety variables (haematology, coagulation, clinical chemistry, and urine analysis).
  - Physical examination.

Secondary endpoints

Part A

- PK parameters:
  - Area under the plasma concentration *vs*. time curve (AUC) from time 0 to infinity (AUC_{inf}) and AUC from time 0 to the time of the last quantifiable concentration (AUC_{last},).
  - Plasma half-life associated with the terminal elimination phase ($T_{½(z)}$), maximum plasma concentration (C_{max}), and time to C_{max} (T_{max}).
  - Total clearance of the drug from plasma following oral administration (CL/F) and apparent volume of distribution associated with the terminal elimination phase (V_z/F).
  - % of dose excreted unchanged in urine and renal clearance.
  - Relative bioavailability of C106 in fasted versus fed conditions.
- Dose proportionality after a single oral dose based on AUC_{inf} and C_{max}.

Part B

- PK parameters after the first dose:
  - AUC over the dosing interval (AUC_{tau}), AUC_{inf}, $T_{½(z)}$, C_{max}, T_{max}, CL/F, V_z/F.
- PK parameters after the last dose:
  - AUC at steady state (AUC_{tau}), $T_{½(z)}$, C_{max}, $T_{max,}$ CL/F, V_z/F.
- Dose proportionality (based on AUC_{tau} and C_{max}) and accumulation ratios (based on AUC_{tau} and C_{max}).
- % of dose excreted unchanged in the urine and renal clearance.
- Observed concentration at the end of a dosing interval, immediately before next administration (C_{trough}).

Exploratory endpoints

- Metabolite In Safety Testing (MIST) analysis of the metabolite profile in plasma in comparison with the metabolite profile in plasma from non-clinical safety studies.
- Profile of excreted metabolites in urine. Cardiodynamic ECG parameters.
- Change from baseline in reactive hyperemia index (RHI) and augmentation index (AI) scores at Day 7 as measured by EndoPAT.

Number of subjects planned

Approximately 160 subjects will be screened to achieve 80 randomised subjects.

Part A: 48 subjects will be randomised and dosed in 6 cohorts (Cohorts A1 to A6, each of 8 subjects with 6 subjects receiving C106 and 2 subjects receiving placebo).

Part B: 32 subjects will be randomised and dosed in 4 cohorts (Cohorts B1 to B4, each of 8 subjects with 6 subjects receiving C106 and 2 subjects receiving placebo).

If indicated by emerging data and recommended by the internal safety review committee (iSRC), 2 cohorts (8+8 subjects) may be added to Part A, and 1 cohort (8 subjects) may be added to Part B.

Diagnosis and main eligibility criteria

- Healthy females of non-childbearing potential and healthy males, 18 to 65 years of age.
- Has provided signed informed consent.
- Body mass index (BMI) ≥18.5 and ≤30.0 kg/m^2.
- Agree to use sufficient contraception as defined in this clinical trial protocol (CTP).
- Good general health and fulfilling all the inclusion criteria and none of the exclusion criteria.

Methodology

This is a double-blind, placebo-controlled, within-group randomised, FIH trial in which the safety, tolerability, and PK of orally administered C106 will be assessed in healthy subjects. The trial consists of 2 parts: a SAD part (Part A) and a MAD part (Part B). One cohort participating in Part A will receive C106 under both fasted and fed conditions to investigate the effect of a high-fat meal on the single dose PK of orally administered C106.

Part A (SAD):

In Part A, single, oral doses of C106 will be administered in 6 sequential dose cohorts, each of 8 subjects. Within each cohort, subjects will be randomised to receive either C106 (n=6) or placebo (n=2) in the fasted state. The proposed doses are: 5, 30, 60, 180, 240 and 300 mg C106. Up to 2 additional dose cohorts can be explored based on emerging safety, tolerability and PK of the drug, if recommended by the iSRC. The maximum oral dose in Part A will not exceed 480 mg C106.

Subjects will come for 3 visits to the Clinical Research Unit (CRU). Screening (Visit 1) will take place within 4 weeks of the planned dose (Day -28 to Day -1) and will include the subject's signing of the informed consent and an eligibility check. At Visit 2, subjects will reside at the CRU from Day -1 (the day before investigational medicinal product [IMP] administration) until Day 3 for single dose IMP administration, safety, tolerability, and PK assessments. The subjects must fast for at least 10 hours before until 4 hours after the anticipated dosing time on Day 1. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 1 hour after dosing. The first 2 subjects in each cohort will be dosed in a sentinel fashion, 1 subject will receive C106 and the other will receive placebo as randomised. The subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals. Ambulatory ECG telemetry will be used for cardiac surveillance up to 24 hours after IMP administration. There is immediate access to equipment, qualified staff and an intensive care unit (ICU) in case of an acute emergency. To give sufficient time for observation of any reactions there will be at least 24 hours before dosing of the remaining 6 subjects, who will be dosed in groups of 3 subjects at least 24 hours apart. A final end-of-trial visit (Visit 3) will take place on Day 7 (±2 days) or after early withdrawal.

Cardiodynamic ECG assessments (collect and store) will be performed in all cohorts (except the first cohort A1) where C106 is given in the fasted state (*i.e.*, not in the fed period of the fasted/fed cohort) and will include serial ECG extractions at baseline (prior to dosing) and at the same time points as PK sampling during the first 24 hours post-dose.

The doses given after the starting dose and time points for safety and PK sampling may be adjusted as recommended by the iSRC following evaluation of emerging safety, tolerability, and PK data. If needed, one visit for additional safety and PK assessments may be added based on recommendations from the iSRC.

Before initiating a new dose cohort, all subjects in the previous cohort must have been treated and all available safety, tolerability, and plasma concentration data up until and including 48 hours post dose must have been evaluated by the iSRC. After collection of the last available 48-hour data, there will be at least one week between dose escalations. In case of dosed dropouts, available data for the dropouts will be included in the iSRC evaluation. Based on emerging safety and PK data, the amount of required safety and PK data to be reviewed after a completed cohort might be adjusted.

Part A: food interaction

One dose cohort (planned to be cohort A4) will be selected to investigate any potential food interaction. The predicted maximum exposure in the food interaction cohort (taking into account a possible food interaction effect on the exposure) of the chosen dose level will not exceed the exposure tolerated in previously evaluated cohorts.

Subjects exposed to C106 during fasting conditions in the selected cohort will return to the clinic after a wash-out period of at least 5 half-lives (as determined by evaluation of PK data) to receive a second dose of C106 under fed conditions. In case of dropouts at the selected dose level, subjects may be replaced to guarantee a full cohort size for the food-interaction part of the trial (if considered necessary). Any replacers will receive active treatment. The assessments during fed conditions will be the same as during fasting conditions except that the subjects will consume a U.S. Food and Drug Administration (FDA) recommended high-fat, high calorie breakfast 30 minutes prior to IMP administration and no screening visit will be conducted. Potential replacement subjects will come for a screening visit and perform one fasting period and one fed period.

Part B (MAD):

In Part B, repeated, oral doses of C106 will be administered in 4 sequential dose cohorts. Within each cohort, subjects will be randomised to receive C106 (n=6) or placebo (n=2) in a blinded fashion. One additional dose cohort can be explored based on emerging safety, tolerability and PK of the drug if recommended by the iSRC. The initial dose, dose escalations and dosing schedule will be based on emerging safety, tolerability, and PK data observed in the SAD part of the trial (Part A) and on emerging data from the MAD part. Each dose level during Part B will be selected such that the predicted maximum exposure will not exceed the maximum exposure (based on AUC and C_{max}) in previously evaluated SAD cohorts. The proposed doses are 40, 100, 180 and 240 mg BID. One (1) additional dose cohort can be explored based on emerging safety, tolerability and PK of the drug if recommended by the iSRC. The maximum daily oral dose in Part B will not exceed 480 mg C106 (240 mg BID). Twice daily dosing for 8 days is planned. Based on emerging PK data once daily dosing may be applied if recommended by the iSRC. The number of dosing days may be changed based on PK data from Part A (SAD), with the aim to reach steady state during the dosing period. The treatment duration will, however, not exceed the treatment duration in pre-clinical toxicology studies.

Subjects will come for 3 visits to the CRU. Screening (Visit 1) will take place within 4 weeks of the first dose (Day -28 to Day -1) and will include the subjects signing of the informed consent and an eligibility check. At Visit 2, subjects will reside at the CRU from Day -1 (the day before IMP administration) until Day 10 for 8 days IMP administration, safety, tolerability, and PK assessments. Subjects must fast from 2 hours prior to each IMP administration until 1 hour after. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 1 hour after dosing. On Day 8, only the morning dose will be administered.

The first 2 subjects in each cohort will be dosed in a sentinel fashion, 1 subject will receive C106 and the other will receive placebo as randomised. The subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals. There is immediate access to equipment, qualified staff and an ICU in case of an acute emergency. To give

sufficient time for observation of any reactions there will be at least 24 hours before dosing of the remaining 6 subjects, who will be dosed in groups of 3 subjects at least 24 hours apart. A final end-of-trial visit (Visit 3) will take place on Day 22 (±2 days) or after early withdrawal.

For subjects participating in cohort B4, an assessment of endothelial function using EndoPAT will be performed before the first IMP administration (on Day -1 or 1), and 30±10 minutes after IMP administration on Day 7 (morning or evening). The EndoPAT assessments should be done at approximately the same time of the day on both occasions. Subjects must fast for at least 4 hours prior to the EndoPAT assessment until end of assessment. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 1 hour after dosing.

Besides the starting dose and subsequent doses, also time points for safety and PK sampling may be adjusted as recommended by the iSRC following evaluation of emerging safety, tolerability, and PK data. If needed, one visit for additional safety and PK assessments may be added based on recommendations from the iSRC.

After collection of the last available 10 days data (48 hours after the last dose), there will be at least 2 weeks between dose escalations. Before initiating a new dose cohort, all subjects in the previous cohort must have been treated and all available safety, tolerability, and plasma concentration data up until and including 48 hours post dose must have been evaluated by the iSRC. In case of non-replaced dropouts, available data for the dropouts will be included in the iSRC evaluation. The iSRC may recommend including replacers to be able to make an informed recommendation on the next dose level. Based on emerging safety and PK data, the amount of required safety and PK data to be reviewed after a completed cohort might be adjusted.

Investigational Medicinal Product, dosage and mode of administration

C106 is a potent and selective nonpeptide angiotensin II type 2 receptor (AT_2R) agonist developed by Vicore Pharma. C106 will be administered as an oral solution.

Placebo to C106 is a solution for oral administration, manufactured as the drug without the active pharmaceutical ingredient.

The bulk IMP will be provided to the research clinic as:

- C106 solution for oral administration; 1 mg/mL and 10 mg/mL.
- Placebo to C106, solution for oral administration without the active pharmaceutical ingredient.

Part A: planned dosage: 5, 30, 60, 180, 240 and 300 mg.

Part B: planned dosage: 40, 100, 180 and 240 mg BID.

Duration of treatment

Part A: Single doses of C106/placebo oral solution.

Part B: C106/placebo oral solution for 8 days. In total 15 doses are planned to be administered.

Duration of each subject's involvement in the trial

Part A: Up to 37 days, including a 28-day screening period.

Part B: Up to 47 days, including a 28-day screening period.

Subjects who are administered C106 both in the fasted and the fed state in Part A are expected to participate in the trial for up to 43 days + at least 5 half-lives of C106 (wash-out between fasting and fed IMP administrations).

Safety assessments AEs, ECGs, vital signs, safety laboratory parameters, physical examinations.
Pharmacokinetic assessments Plasma and urine sampling for C106 concentration analysis and subsequent determination of PK parameters.
Exploratory assessments Blood and urine sampling for analysis of C106 metabolites (Part B). Collection of cardiodynamic ECG using a Holter device (Part A fasting, except cohort A1). Endothelial function will be assessed using EndoPAT (Part B, cohort B4).
Statistical methods No formal sample size calculation has been performed. The proposed sample size is considered sufficient to provide adequate information for the trial objectives. A statistical analysis plan (SAP) will be prepared and signed prior to database lock. All quantitative variables will be summarised by assigned treatment (dose cohort or placebo) and time point using standard descriptive statistics. Qualitative variables will be summarised by assigned treatment and time point by means of absolute and relative frequencies. Assessment of dose proportionality will be performed based on AUC_{inf} and C_{max} (Part A) and based on AUC_{tau} and C_{max} (Part B) using a power model.
Trial reporting After completion of the trial, an International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 compliant clinical trial report (CTR) will be prepared.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
ADL	Activities of daily living
AE	Adverse event
AI	Augmentation index
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AT_1R	Angiotensin II type 1 receptor
AT_2R	Angiotensin II type 2 receptor
AUC	Area under the plasma concentration *vs*. time curve
AUC_{inf}	AUC from 0 to infinity
AUC_{last}	AUC from 0 to the time of the last quantifiable concentration
AUC_{tau}	AUC to the end of the dosing period
BP	Blood pressure
bpm	Beats per minute (unit for pulse measurement)
BMI	Body mass index
C106	Compound 106
CA	Competent authority
CDC	Centres for Disease Control and Prevention
CIOMS	Council for International Organisations of Medical Sciences
CL/F	Apparent total body clearance following extravascular administration
C_{max}	Maximum plasma concentration
CRP	C-reactive protein
CTP	Clinical trial protocol
CTR	Clinical trial report
CTC	Clinical Trial Consultants AB
CTCAE	Common terminology criteria for adverse events
CTC PV	CTC's pharmacovigilance departments
CV	Coefficient of variation
DMP	Data management plan
DSUR	Development safety update report
ECG	Electrocardiogram

ECM	Extracellular matrix
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EMA	European Medicines Agency
EPQT	Expert precision QT
FDA	U.S. Food and Drug Administration
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GDPR	General data protection regulation
GMP	Good manufacturing practice
Hb	Haemoglobin
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent ethics committee
IME	Important medical event
IMP	Investigational medicinal product
IPF	Idiopathic pulmonary fibrosis
ISF	Investigator site file
iSRC	Internal safety review committee
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LLOQ	Lower limit of quantification
MEC	Molar extinction coefficient
MedDRA	Medical dictionary for regulatory activities
MIST	Metabolite In Safety Testing
MPA	Medical products agency
MAD	Multiple-ascending dose
NCA	Non-compartmental analysis
NIH	National Institute of Health
NOAEL	No observed adverse effect level

PCLuS	Precision cut lung slices
PII	Personally Identifiable Information
PD	Pharmacodynamic
PK	Pharmacokinetic
PR interval	(ECG) The time from the onset of the P wave to the start of the QRS complex
PT	Preferred term
QA	Quality assurance
QC	Quality control
QRS interval	(ECG) The time required for stimulus to spread through the heart's ventricles
QT interval	(ECG) The time from the beginning of the QRS complex to the end of the T wave
QTcF	(ECG) Corrected QT interval by Fredericia
RAS	Renin-angiotensin system
RBC	Red blood cell
RHI	Reactive hyperemia index
RSI	Reference safety information
SAD	Single-ascending dose
SAR	Serious adverse reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SOC	System organ class
SOP	Standard operating procedures
SPF	Sun protection factor
SuHx	Sugen-hypoxia
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file
T_{max}	Time of occurrence of C_{max}
$T_{½(z)}$	Plasma half-life associated with the terminal elimination phase
UVA	Ultraviolet A
UVB	Ultraviolet B
V_z/F	Apparent volume of distribution following extravascular administration
WBC	White blood cell
WHO	World Health Organisation

4 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

4.1 Medical emergencies contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the trial. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such. Detailed SAE reporting procedures are described in Section 11.3.1.13.

In the case of a medical emergency, the Investigator may (during business hours) contact the Medical Monitor (Table 4.1-1).

Table 4.1-1 Medical emergencies contact

Name	Function in the trial	Telephone number and e-mail
[redacted]	[redacted]	[redacted]

5 INVESTIGATOR AND TRIAL ADMINISTRATIVE STRUCTURE

Sponsor

Vicore Pharma AB
Kornhamnstorg 53
SE-111 27 Stockholm, Sweden

Sponsor's Medical Representative

[redacted]

Sponsor's Project Manager

[redacted]

Clinical conduct

CTC Clinical Trial Consultants AB (CTC)
Uppsala University Hospital,
Entrance 85, 2nd level
SE-751 85 Uppsala, Sweden

Principal Investigator

[redacted]

Trial management

CTC
Dag Hammarskjölds väg 10B
SE-752 37 Uppsala, Sweden

Clinical Research Manager

[redacted]

Biostatistician

[redacted]

Pharmacokineticist:

[redacted]

Medical writer

[redacted]

Medical monitor

[redacted]

Laboratories (Safety)

Clinical Microbiology
Dag Hammarskjölds väg 38
SE-752 37 Uppsala, Sweden

Clinical Chemistry and Pharmacology
Uppsala University Hospital
Entrance 61, 2nd level
SE-751 85 Uppsala, Sweden

Laboratory (Bioanalysis)	Lablytica Life Science AB Virdings allé 18 SE-754 50 Uppsala, Sweden
Laboratory (Metabolite In Safety Testing [MIST])	Admescope Forskargatan 20J SE-151 36 Södertälje, Sweden
Investigational medicinal product (IMP) manufacturing, packaging, labelling, and release	Ardena Kleimoer 4 B-9030 Mariakerke Belgium
Pharmacy	Apoteket AB Clinical Trial Unit Dag Hammarskjölds väg 18, Entrance C7 SE-751 85 Sweden
Expert precision QT (EPQT) collect & store	Clario Peterborough Business Park Lynch Wood, Peterborough PE2 6FZ, United Kingdom
Electronic data capture (EDC) system provider	Viedoc Technologies AB Stationsgatan 23 SE-753 40 Uppsala, Sweden

Signatures are provided in Section 19.

6 INTRODUCTION

6.1 Background

6.1.1 *Idiopathic pulmonary fibrosis*

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, irreversible, and devastating interstitial lung disease with no existing cure [1, 2]. IPF is characterised by a progressive deposition of extracellular matrix (ECM) proteins and fibrous tissue in the lungs, resulting in destruction of lung architecture and reduced lung capacity [3]. The aetiology of IPF is unknown. However, several risk factors are reported to be associated with development of IPF including cigarette smoking, environmental exposures, microbial pathogens, and genetic factors [4].

Symptoms of IPF include shortness of breath, fatigue, and a dry intractable cough. IPF is usually lethal and death is most commonly caused by acute or subacute respiratory failure due to progression of lung fibrosis [5]. Increasing pulmonary vascular pressure often leads to pulmonary hypertension and subsequently to heart failure. The prevalence of pulmonary hypertension in patients with IPF is between 32 and 85% [6]. The prognosis of IPF is poor, with an estimated life expectancy of 3-5 years after diagnosis which is shorter than many malignancies [7]. The mortality is on the rise globally [8].

Worldwide, approximately 3 million people are living with IPF and it is classified as an orphan disease within the EU and the USA. The incidence of IPF is estimated to be 2.8 to 19 per 100,000 people per year and increases with age. Debilitating symptoms typically appear between the ages of 50 and 70 years and, while the disease is most common in men, the number of cases in women is increasing [9].

IPF is often associated with comorbidities including lung cancer, pulmonary hypertension, chronic obstructive pulmonary disease, and ischaemic heart disease [10]. The impact of comorbidities on the prognosis of IPF is not well established, however mortality has been reported to be higher in patients with the comorbidities mentioned above, and treatment of comorbidities may therefore contribute to improved survival and quality of life [10].

Currently, there is no cure for IPF and treatment options are limited. Two antifibrotic drugs, nintedanib and pirfenidone, are approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) and conditionally recommended for the treatment of patients with mild to moderate IPF [10]. Both nintedanib and pirfenidone slow disease progression, but they are not curative and cause significant, primarily gastrointestinal, side effects [10]. Access to nintedanib and pirfenidone can also be challenging for patients. In the UK, nintedanib and pirfenidone are only recommended as an option for treating IPF if the patient has a forced vital capacity (FVC) between 50% and 80% of predicted, and treatment is stopped if disease progresses (a confirmed decline in percent predicted FVC of 10% or more) in any 12-month period [11].

Lung transplantation is rare; just 214 lung transplants were carried out for pulmonary fibrosis in England in 2017-18 [12], and it is only recommended in a small group of patients with moderate to severe IPF. Median post transplantation survival in IPF is estimated to 4.5 years [13]. However, patients are often referred late in the course of the disease and may die while waiting for a transplant [1].

Thus, a major medical unmet need still exists for finding more safe and efficacious treatment for IPF targeting not only disease progression, but also comorbidities including pulmonary hypertension.

6.1.2 *Product characteristics, mechanism of action and rationale for C106 treatment of idiopathic pulmonary fibrosis*

Compound 106 (C106) is a low molecular weight, orally available, high affinity angiotensin II type 2 receptor (AT_2R) agonist, and an analogue to Vicore Pharma's AT_2R agonist C21.

Angiotensin II (AngII) is the major effector peptide of the renin-angiotensin system (RAS) and exerts key roles in multiple physiological processes including regulation of blood pressure, fluid homeostasis, cellular growth, differentiation, proliferation, migration, apoptosis as well as ECM remodelling and inflammation (reviewed in [14, 15].

AngII mediates its effects by binding to angiotensin II type 1 receptors (AT_1R) and angiotensin II type 2 receptors (AT_2R). The AT_1R mediates the classical effects of AngII such as cellular growth, migration, proliferation, fibrogenesis, inflammation, and vasoconstriction and is expressed in many tissues, whereas the AT_2R mediates antifibrotic, antiproliferative, anti-inflammatory, and vasodilatory effects. The AT_2R is abundantly expressed in embryonic tissue and, under normal conditions, only at low levels in most tissues in healthy adults [16, 15]. However, the AT_2R is relatively highly expressed in the normal adult human lung, in particular by the multifunctional alveolar type 2 cell [17], and can be upregulated in response to tissue damage and various diseases including IPF [18, 19, systemic sclerosis [19], vascular injury [20] and cardiac fibrosis [21], indicating an inducible tissue-protective role for AT_2Rs during pathological conditions.

Several studies suggest that AngII and AT_1Rs are involved in the pathogenesis of lung fibrosis, including IPF [22, 23, 24]. The role of the AT_2R in IPF is not fully established, but a protective role is likely considering that the lung AT_2R is upregulated in IPF and mediates antifibrotic effects such as reducing fibroblast proliferation, cell growth, and ECM synthesis, in addition to vasodilatory effects [18, 22, 25].

An upregulation of the AT_2R was demonstrated in septal and vascular areas [19], in fibrotic fibroblasts from human IPF lungs [18], as well as in animal models of lung fibrosis and hyperoxia-induced lung injury [18, 26, 27]. In these experiments, the surface expression of AT_2R on interstitial fibroblasts was increased after lung injury when compared to healthy animals, whereas the surface expression of the AT_1R was similar in fibrotic and normal fibroblasts. Interestingly, AngII-induced proliferation of fibroblasts was mediated primarily via the AT_1R in healthy fibroblasts whereas AngII induced antiproliferation via an AT_2R-dependent mechanism in fibrotic fibroblasts, demonstrating a shift in the response to AngII in fibrotic lungs, probably due to an upregulation of AT_2R [18].

Vicore Pharma's potent and selective AT_2R agonist C21 is currently in phase 2 clinical development for IPF, and it has previously been demonstrated in 2 different animal models that C21 reduces pulmonary fibrosis. In the first study, pulmonary hypertension and fibrosis were induced in rats by a monocrotaline injection, and it was found that treatment with C21 for 2 weeks not only prevented, but also reversed pulmonary interstitial and perivascular fibrosis [28]. This effect was associated with significant improvements in right heart function and decreased pulmonary vessel wall thickness. In a second study, pulmonary fibrosis and associated pulmonary hypertension were induced in rats by bleomycin treatment [29]. Treatment with C21 for 2 weeks almost completely prevented the progression of lung

fibrosis and, in addition, reduced pulmonary hypertension and muscularisation of the pulmonary vessels, and normalised cardiac function.

Pulmonary hypertension, group III of the international aetiological classification, is a frequent and severe complication of interstitial lung diseases, especially IPF [30]. In the Sugen-hypoxia (SuHx) model of group I pulmonary arterial hypertension (PAH), but also a useful adjunct to group III pulmonary hypertension, C21 caused a robust reduction of the SuHx-induced increase in endothelial cell hyperplasia and pulmonary hypertension (IPST20200130- 1).

Thus, C106 is believed to represent a novel treatment of fibrotic diseases such as IPF capable of reducing pulmonary inflammation, proliferation, fibrosis, and vasculopathy, like the analogue C21.

6.1.3 *Non-clinical pharmacodynamics*

6.1.3.1 Primary pharmacodynamics

C106 is a selective nonpeptide AT_2R agonist with AT_2R Ki= 3.3 nM and AT_2R IC_{50}=6.5 nM (100052430). The binding of C106 to AT_1R has been evaluated in several studies and inhibition of 18.2% and 48.4% at 1 µM and 86.2% at 10 µM have been demonstrated. In comparison, binding of C106 to AT_2R was determined to be 97% at 0.1 µM (TW04-0011337) and 100% at 1 µM and 10 µM (100052430).

C106 demonstrated antifibrotic effects in a human *ex vivo* model of IPF, precision cut lung slices (PCLuS), by reducing the secretion of the pro-fibrotic factors' collagen 1a1 and TGF- β1, suggesting that C106 has antifibrotic potential in IPF.

6.1.3.2 Secondary pharmacodynamics

Upon evaluating binding affinity, C106 did not show any significant binding affinity to the 75 receptors and ion channels tested or any significant inhibition of the 12 enzyme and uptake assays tested, when tested at 1 µM (100059310).

6.1.4 *Non-clinical pharmacokinetics and drug metabolism*

Pharmacokinetic studies of C106 have been performed in rats following oral and intravenous administrations and in dogs after oral administration. The oral route is the intended route of administration in the clinical development program. *In vitro* studies have been conducted to evaluate plasma protein binding, metabolic stability, metabolite identification, and involvement of enzymes to investigate the potential of metabolic interactions.

Following intravenous administration in rats, C106 is classified as an intermediate clearance compound with an intermediate terminal half-life of about 2 h.

C106 was absorbed rapidly after single and repeated oral administration with maximum plasma concentration C_{max} reached within 1-4 h in rats and dogs, followed by a prolonged elimination from the plasma and an elimination half-life ($t_{1/2}$) of 2.9 to 11 h in rats and 1 to 4.6 h in dogs. No accumulation of C106 was observed following repeated once daily oral administration for up to 28 days in rats and dogs, while a trend for a lower systemic exposure was seen in rats on Day 28, and at the highest dose in dogs. The oral bioavailability was estimated to 30-50% after a single dose of 10 mg/kg in rats.

The plasma exposure of C106 following oral administration in both rats and dogs was dependent on dose. The exposure in terms of C_{max} and area under the plasma concentration *vs*. time curve (AUC) in rats increased more than dose-proportionally following repeated administration of doses up to 40 mg/kg. Overall, a trend for higher exposures was seen in female rats compared to male rats after a single administration, but not after repeated administrations.

In dogs, the plasma exposure increased more than dose-proportionally following repeated administration of doses up to 40 mg/kg, although the supra-proportional increase was less pronounced on Day 28 than on Day 1. Overall, there was no significant sex difference in dogs in the exposure to C106 with no apparent differences seen in absorption or elimination for Day 1 and Day 28.

The plasma protein binding was high in all species, with dogs having the lowest protein binding (on average 97.5% in dog, 99.8% in rat and 99.6% in human), and independent of C106 concentration in the range of 0.1-50 µM.

The metabolism of C106 was slow in human *in vitro* studies with an intrinsic clearance of 4.0 µL/min/10^6 hepatocytes, and with 11 metabolites being formed *in vitro*. All metabolites formed in human hepatocytes were also formed in hepatocytes from the animal species used in the safety evaluation (rat and dog), except for a minor metabolite formed by oxidation of the imidazole ring and hydrolysis of the methyl formate chain. The main metabolic pathways in mouse, rat, dog, monkey, and human included i) oxidation, ii) hydrolysis of methyl formate, iii) dehydrogenation, and combination of these pathways. No conjugated metabolites were identified in any species.

6.1.5 *Non-clinical safety pharmacology*

Non-clinical safety pharmacology has been studied in the rat and the dog.

Overt central and peripheral effects

Potential side-effects of single doses of C106 on the central and peripheral nervous system (6, 15, 40 mg/kg; orally by gavage) were investigated in an Irwin test in female Sprague Dawley rats (2021-0358). No effects on either general behaviour including home cage observations, open field observations and reflexes, or body temperature were observed at any of the doses up to 40 mg/kg. Therefore, the no observed adverse effect level (NOAEL) in the study was determined to be 40 mg/kg.

Effects on the cardiovascular system

Cardiovascular effects of C106 treatment were observed in Beagle dogs. The main findings were increased blood pressure and electrocardiogram (ECG) aberrations. Increases in systolic and diastolic arterial pressure were observed at doses of 10 to 40 mg/kg in a single dose telemetry study. The heart rate showed a slight, yet statistically significant, increase between 45 and 180 minutes after administration. The ECG intervals RR and QT were decreased at all doses tested (10-40 mg/kg), and these changes were compatible with the increase in heart rate. In addition, second degree atrioventricular (AV) block was observed as repeated incidences at different time-points following administration of 10 to 40 mg/kg.

No toxicologically relevant changes in body temperature were observed following treatment with C106 at any dose tested.

In addition, upon evaluating binding affinity to the human potassium channel hERG, C106 did not show any significant binding at 1 μM.

Effects on the respiratory system

The effects of single doses of C106 (6, 15, and 40 mg/kg) on the respiratory system were examined by plethysmography in female SD rats (2021-0361). No treatment-related effects on respiration (including respiratory rate, tidal volume, and minute volume) or adverse clinical signs were observed at any of the doses up to 40 mg/kg during a 4-hour recording period. Therefore, the NOAEL in the study was determined to be 40 mg/kg.

6.1.6 *Toxicology*

The toxicity of C106 has been evaluated in single and repeated dose oral gavage toxicology studies of up to 4 weeks duration in rat and dog, as well as in genotoxicity studies.

In the rat, the main toxicological findings were treatment-related histological changes in the heart, the aorta, and the kidney in animals of both sexes. These findings included multifocal inflammatory cells infiltration of the myocardium and of the adventitia of aorta after 4 weeks of treatment and occurred at 20 and 40 mg/kg/day in males, and at 15 (aorta, only) and 25 mg/kg/day in females and were in general more pronounced in males than in females. In 4 males in the high dose group (40 mg/kg/day), a concomitant presence of myocardial fibrosis was also observed. In the kidney, changes of cortical tubular basophilia, interstitial inflammatory cell infiltration, and tubular dilation were observed in all 3 treatment groups in both male (10, 20, and 40 mg/kg/day) and female (6, 15, 25 mg/g/day) animals and occurred in a dose-dependent manner in incidence and severity. Treatment-related histological changes were also observed in the adrenal glands in 2 male and in 2 female animals administered 40 and 25 mg/kg/day, respectively, and were considered non-adverse. After the recovery period (2 weeks after end of treatment) in the high dose groups, findings in the kidneys and heart were still observed, whereas the findings in the aorta and in the adrenal glands were reversible and not observed after the recovery period.

After 7 days of treatment, treatment-related histological changes were also observed in the kidneys and the heart. In the kidney, cortical tubular basophilia was observed in animals administered 40 mg/kg. Cortical tubular dilatation was observed in control males and in female animals in the 40 mg/kg group. In the heart, atrioventricular myocardial necrosis of cardiomyocytes with mononuclear inflammatory cell infiltration was observed in animals administered 40 mg/kg.

A minimal to moderate reduction in body weight gain and food consumption was observed after 4 weeks of treatment of the high dose in animals of both sexes.

In the dog, the main toxicological findings were single and repeated incidences of second-degree AV-block after single and repeated dosing, respectively. Single episodes of AV block were reported in 1 male after a single dose of 30 mg/kg and in 1 male and 1 female after a single dose of 90 mg/kg. Repeated incidences of second-degree AV-block were reported in 1 male dog after 7 days of treatment with 60 mg/kg/day and in 1 male dog after 4 weeks of treatment with 40 mg/kg/day. These ECG abnormalities were considered indicative of arrhythmias.

After 4 weeks of treatment in the dog, treatment-related changes were observed in the adrenal glands. The findings consisted of a decrease in lipid vacuolation in the cells of the zona fasciculata, and an increase in vacuolation of the cells of the zona glomerulosa in both sexes.

There are no indications of mutagenic or genotoxic potential of C106.

6.1.7 *Clinical experience*

This is a first-in-human (FIH) trial, C106 has not yet been studied in humans.

The safety of activating the AT_2R has previously been evaluated with the AT_2R agonist C21 in 3 completed Phase 1 trials (C21-001-16, C21-002-16, and C21-003), in 1 completed Phase 2 trial in hospitalised patients with COVID-19 (VP-C21-006) and in 1 completed Phase 2 trial in patients with Raynaud's phenomenon secondary to SSc (VP-C21-004) with a total of 146 subjects exposed to at least one oral dose of C21 in these trials. Across the trials, C21 was generally well tolerated at daily doses up to 200 mg, whereas doses of 200 mg twice daily (in total 400 mg daily) for 8 days resulted in reversible hair loss in 6 out of 6 subjects occurring within 2 weeks after end of dosing and improving within 8 weeks (C21-003). In addition, there is one ongoing IPF phase 2 trial with C21 (VP-C21-005). After administration of 100 mg C21 twice daily, mild to moderate "hair fall or hair loss" has been reported in 5 subjects in this trial, where 4 out of the 5 cases have resolved and 3 out of 5 subjects continued treatment with C21. The observed hair loss was considered related to C21 treatment and due to a pharmacological effect of stimulation of the AT_2R. This adverse reaction was not observed at lower dose levels in any of the completed trials. For additional information, see Section 6.3.

Across the Phase 1 trials, the most commonly observed treatment-emergent adverse event (AE) considered related to treatment was headache. C21 is currently in Phase 2 clinical development for treatment of IPF and in Phase 3 clinical development for treatment of moderate to severe COVID-19.

In the present trial, 24 subjects have been dosed with C106 in 4 single dose cohorts (5, 30, 60 and 180 mg). In each cohort, 8 subjects have been administered C106 or placebo in a 3:1 ratio. The interim PK analysis showed that C106 had a fast absorption with a T_{max} at 20-40 minutes and a mean terminal half-life ($T_{1/2}$) of approximately 11 hours. The plasma exposure of C106 was lower than expected at all dose cohorts evaluated, and the dose proportionality was non-linear. Interim PK analysis of plasma exposure in terms of C_{max} and AUC_{inf} is presented in Table 8.3-2 in Section 8.3.1.

C106 has been generally well tolerated, without clinically significant findings regarding AEs, ECG, safety laboratory assessments and physical examinations. In total 2 AEs have been reported as possibly related to blinded IMP, both were transient and mild in intensity. In conclusion, the overall safety and tolerability evaluation has not identified any safety signals in the completed cohorts.

6.2 Trial rationale

C106 is being developed for oral treatment of fibrotic diseases, including IPF. C106 is an analogue to Vicore Pharma's AT_2R agonist C21, as described in Section 6.1.2, with expected lower risk of drug-drug interactions due to cytochrome P450 (CYP) inhibition than C21. It is believed to represent a novel treatment capable of reducing pulmonary inflammation, proliferation, fibrosis, and vasculopathy.

This Phase 1 clinical trial (VP-C106-101) is a FIH, double-blind, placebo-controlled, within-group, randomised, single-centre trial will be performed to evaluate safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending oral doses of C106 in healthy male

and female subjects. The results are expected to support the design of further studies, both in healthy volunteers and in patients.

The AT_2R agonist C21 has been shown to increase forearm blood flow in healthy subjects after intraarterial administration (VP-C21-009) and also to improve blood flow in Raynaud's Phenomenon in patients with severe vasculopathy due to systemic sclerosis (VP-C21-004). An exploratory assessment of endothelial function has been added to Part B, cohort B4 to evaluate if an improved vasodilator response to reperfusion can be achieved in healthy volunteers by stimulating the AT_2R with C106.

The rationale for the trial design is outlined in Section 8.2.

6.3 Risk/benefit assessment

This trial involves the first administration of C106 to humans, and there are no previous data on the effects of the drug in humans. It is therefore difficult to make predictions about possible adverse reactions. The healthy volunteers in this trial will have no medical benefit from participation, and their safety and wellbeing are hence of outmost importance.

In pre-clinical safety pharmacology and toxicity studies, increased blood pressure and heart rate were observed in the dog following administration of single doses of C106 at 10 to 40 mg/kg. ECG findings comprised a dose-dependent increase in arterial blood pressure (systolic, diastolic, and mean) and a slight statistically significant increase in heart rate at all doses tested, reduced RR and QT intervals, compatible with the increased heart rate and without variation in QTc, but also increases in PR intervals and repeated incidences of second-degree AV block, see Section 6.1.5 and Section 6.1.6 for details. Similar cardiovascular effects were previously observed with the C106 analogue C21 in toxicity and safety pharmacology studies in dogs. C21 has undergone a comprehensive clinical program, including Phase 1 and Phase 2 human clinical trials, with extensive cardiovascular monitoring. In contrast to the cardiovascular findings in dogs, no clinically significant findings related to blood pressure, heart rate or second-degree AV block were observed in these C21 human clinical trials or in studies in Cynomolgus monkeys, despite much higher exposure of C21 (both in terms of C_{max} and AUC) in the human clinical trials compared to the exposure inducing the adverse cardiovascular effects in dogs. Altogether, these results indicate that the cardiovascular effects observed with C21 in the dog were due to a species-specific mechanism. In analogy, the cardiovascular effects observed with C106 are hence assumed to be of no relevance to human clinical conditions. However, subjects in this trial will be frequently monitored for changes in blood pressure and ECG, including ambulatory telemetry monitoring in the Single Ascending Dose (SAD) part, from 30 min pre-dose until 24 hours post-dose. In addition, subjects with a prolonged QTcF or QRS, or a PR interval outside of reference ranges, clinically significant cardiac arrhythmias, or any clinically significant abnormalities in the resting ECG at the time of screening will not be included in the trial.

In view of the inflammatory findings observed after administration of C106 in the rat, see Section 6.1.6, and not in the dog, it has been demonstrated in several studies that in general, the rat seems to be more prone to develop inflammatory cell infiltration in a variety of organs than other species (*e.g.*, [31]). In addition, the rat has higher expression of pro-inflammatory mediators and lower levels of anti-inflammatory mediators compared to other species [32], and the pro-inflammatory response in rats compared to other species including mouse, hamster, primate, and human has been characterised as "abnormally high" [33]. In this context, even though C106 is characterised as an AT_2 receptor agonist, C106 also possesses

weak AT_1 receptor agonist properties, and the expression of AT_1 and AT_2 receptors vary widely between species and also between various organs within a species [15]. A rat-specific altered balance between expression of AT_1 versus AT_2 receptors may contribute to explain the infiltration of inflammatory cells in certain tissues in rats. This assumption is supported by quantitative autoradiography studies mapping AT receptor subtypes [34, 35].

The absence of infiltration of inflammatory cells in the dog fits also well with the suggestion that the dog has been demonstrated to be less prone to pro-inflammatory reactions and proliferative changes in various organs as compared to the rat [36]. Altogether, the results suggest that the observed infiltration of inflammatory cells in the kidney, heart, and aorta in the rat is species-specific to the rat and most likely of no relevance for the current trial. Yet, markers of inflammation (C-reactive protein [CRP] and white cell counts with differentials) will be monitored throughout both parts of the trial.

A Phase 1 clinical trial with C21 reported reversible hair loss in 6 healthy subjects exposed to 200 mg C21 twice daily for 8 days (400 mg per day) (C21-003). The events included hair loss on the head and the body and occurred on average 11 (ranging from 8 to 14) days after end of dosing. Regrowth of the hair was observed in all subjects within 8 weeks after end of dosing. The observed hair loss was considered related to treatment with C21 and was possibly due to a pharmacological effect of stimulation of the AT_2R. No cases of hair loss have been reported at dose levels up to 100 mg C21 twice daily for 7 days or after single doses of 200 mg in any of the completed, randomised, controlled clinical trials with C21.

As described in the current version of the IB (cut-off date 15-Mar-2022), mild to moderate "hair fall or hair loss" has been reported in 5 subjects in the ongoing, open-label IPF phase 2 trial after administration of 100 mg C21 twice daily (VP-C21-005). 4 out of the 5 cases have resolved; 3 out of 5 subjects continued treatment with C21. The characteristics and nature of the 'hair fall or hair loss' reported in this trial appear to be different from the hair loss reported in the phase 1 trial, and the relationship to treatment is unclear.

Although the mechanism for the reversible hair loss is not known, it cannot be excluded that it is a potential class effect related to high dose AT_2R stimulation. It is therefore a risk that the subjects who participate in Part B of the current trial may experience hair loss. Hair loss of moderate intensity (*i.e.*, Common Terminology Criteria for Adverse Events [CTCAE] grade 2) in 2 subjects assessed as related to the IMP administration has hence been included as a stopping criterion for dose escalation, see Section 8.3.5.

The phototoxicity of C106 has not been investigated but based on the molar extinction coefficient (MEC) value obtained from absorbance studies a phototoxic potential cannot be excluded. Thus, sun protection, as defined in Section 9.6.1, should be used during the study.

In both parts, subjects will be admitted to the clinic the day before each residential stay (Day -1). In Part A (SAD), subjects will remain in the clinic until 48 hours after the administration of the Investigational medicinal product (IMP). In Part B, subjects will be admitted to the clinic during the whole dosing period and for 48 hours after the last dose. During stays at the clinic, subjects will be closely monitored by medical staff. Sentinel dosing will apply for the first subjects in both parts. Visits at the clinic may be prolonged in case the Investigator finds it medically warranted for safety reasons.

The selection of starting-dose and dose-escalation steps represents a careful approach to administer the drug for the first time in humans, see Section 8.3. An internal safety review committee (iSRC) will monitor emerging safety, tolerability and PK data over the course of the trial and will give a recommendation on the next dose level prior to any dose escalation. In

Part A, after collection of the last 48 hours data, there will be at least 1 week between dose escalations. In Part B (Multiple Ascending Dose [MAD]), after collection of the last available 10 days data (48 hours after the last dose), there will be at least 2 weeks between dose escalations. Any indication of hair loss emerging after the 48-hour data cut off will be considered by the iSRC at the iSRC meeting.

Overdosing is not likely to occur since all IMP will be administered by site personnel under medical surveillance. In cases of accidental overdose, standard supportive measures should be adopted as required. For further information regarding overdosing, refer to Section 11.3.1.17.

Each volunteer will be provided with a subject participation card with information about the subject participation in a trial, see Section 14.4.

The Principal Investigator at the research clinic will ascertain that adequate facilities and procedures are available to handle emergency situations in case they occur during the trial. The medical staff at CTC have extensive experience from early Phase 1 and FIH studies and there are adequate procedures in place to handle unexpected and expected adverse reactions in the trial subjects. The research clinic is located adjacent to Intensive Care Unit (ICU) at the University Hospital in Uppsala. CTC has a separate agreement with the ICU for support in case of emergencies. CTC has been regularly inspected by the Swedish Medical Products Agency (MPA) and is authorised to conduct FIH studies.

Besides the risks related to the IMP as described above, there may also be risks related to the medical devices used in the trial *e.g.*, indwelling venous catheters. However, these are devices that are used in routine medical care and the risk associated with their use is considered low and ethically justifiable. EndoPAT is a non-invasive medical device used to assess endothelial function. During the assessment, a blood-pressure cuff is used to achieve and maintain arterial occlusion for 5 minutes. Inflating the cuff might cause some stress and discomfort to the subject. Other trial specific evaluations and sampling procedures, like blood-pressure measurements using a blood pressure cuff and frequent blood-sampling, may cause transient discomfort but the risk is deemed to be low and ethically justifiable.

Overall, the combined safety data from the pre-clinical studies have not revealed any safety issues that would outweigh the expected benefits of the trial. While keeping the above-mentioned risk factors at a minimum level in order to not expose the subjects participating in the trial for risks that would not be ethically justifiable it is concluded that the planned trial assessments are considered sufficient to meet the scientific and medical goals for the trial. It is therefore concluded that the potential benefits from the trial will outweigh the potential risks for the treated subjects.

More detailed information about the known and expected benefits and risks are found in current version of the Investigator's Brochure (IB).

6.3.1 *Risk assessment with regards to the COVID-19 pandemic*

Current recommendations from the authorities will be considered on a day-to-day basis and a continuous risk evaluation will be made to assess how the COVID-19 pandemic is affecting the study conduct and the safety of the study subjects.

Any identified risks in terms of subject safety, trial performance and data quality/integrity will be documented in a risk log as part of the Sponsor's trial master file (TMF).

The recommendations from the EMA [37, 38] as well as the Swedish Medical Products Agency (MPA) [39] regarding the conduct and management of clinical trials during the COVID-19 pandemic will be taken into consideration.

7 TRIAL OBJECTIVES AND ENDPOINTS

7.1 Objectives and endpoints

The objectives, endpoints and assessments are summarised in Table 7.1-1. The exploratory endpoints (MIST, urine metabolites and endothelial function) may be reported separately from the clinical trial report (CTR). Cardiodynamic ECG data will be stored for potential future evaluation and will thus not be included in the CTR.

Table 7.1-1 Objectives and endpoints

Objective	Endpoint	Assessment(s)
Primary		
To evaluate the safety and tolerability of single and multiple oral doses of C106 in healthy subjects.	Treatment emergent AEs and SAEs	AE reporting and questioning (Section 11.3.1)
	Clinically significant changes in 12-lead electrocardiograms (ECGs), vital signs, laboratory safety variables (haematology, coagulation, clinical chemistry and urine analysis), and physical examinations.	12-lead ECG (Section 11.3.2), Vital signs (Section 11.3.4), Blood sampling for clinical chemistry and haematology, urine sampling for urinalysis (Section 11.3.5), Physical examination (Section 11.3.6).
Secondary		
To characterise the pharmacokinetics (PK) of single and multiple oral doses of C106 in plasma and urine of healthy subjects.	Part A • AUC from time 0 to infinity (AUC_{inf}) and AUC from time 0 to the time of the last quantifiable concentration (AUC_{last},). • Plasma half-life associated with the terminal elimination phase ($T_{½(z)}$), C_{max} and time to C_{max} (T_{max}). • Total clearance of the drug from plasma following oral administration (CL/F) and apparent volume of distribution associated with the terminal elimination phase (Vz/F). • Dose proportionality after a single oral dose based on AUC_{inf} and C_{max}. • % of dose excreted unchanged in urine. • Renal clearance.	Pharmacokinetic sampling and analysis (Section 11.4.1 and Section 11.4.2).
	Part B • PK parameters after the first dose: o AUC over the dosing interval (AUC_{tau}), AUC_{inf}, $T_{½(z)}$, C_{max}, T_{max}, CL/F, V_z/F. • PK parameters after the last dose: o AUC at steady state (AUC_{tau}), $T_{½(z)}$, C_{max}, T_{max}, CL/F, V_z/F . • % of dose excreted unchanged in the urine. • Renal clearance	

	• Dose proportionality (based on AUC_{tau} and C_{max}) and accumulation ratios (based on AUC_{tau} and Cmax). • Observed concentration at the end of a dosing interval, immediately before next administration (C_{trough}).	
To evaluate the effect of a high fat meal on the single oral dose PK of C106 in healthy subjects (Part A).	• PK parameters as for Part A. • Relative bioavailability of C106 in fasted versus fed conditions.	
Exploratory		
To evaluate the metabolite profile of C106 in plasma of healthy subjects at steady state (Part B).	Metabolite In Safety Testing (MIST) analysis of the metabolite profile in plasma in comparison with the metabolite profile in plasma from non-clinical safety studies.	MIST (Section 11.5.1).
To estimate the excreted C106 and its metabolites and the metabolite profile of C106 in urine of healthy subjects at steady state (Part B).	Profile of excreted metabolites in the urine.	Urine sampling and analysis (Section 11.5.2).
To collect and store ECG data for potential future evaluation of the effect of C106 on ECG parameters, including concentration-QTc analysis using Expert Precision QT (EPQT) assessment (Part A).	Cardiodynamic ECG parameters.	EPQT assessment (Section 11.5.3).
To evaluate the pharmacodynamic (PD) effect of C106 on endothelial function in healthy subjects at steady state (Part B, cohort B4).	Change from baseline in reactive hyperemia index (RHI) and augmentation index (AI) scores at Day 7 as measured by EndoPAT.	EndoPAT assessment (Section 11.5.4).

8 TRIAL DESIGN

8.1 Overall trial design and schedule of events

This is a FIH, double-blind, placebo-controlled, within-group randomised, trial designed to evaluate the safety, tolerability and PK of single and multiple ascending oral doses of C106 in healthy females of non-childbearing potential and healthy males.

The trial will be conducted in 2 parts:

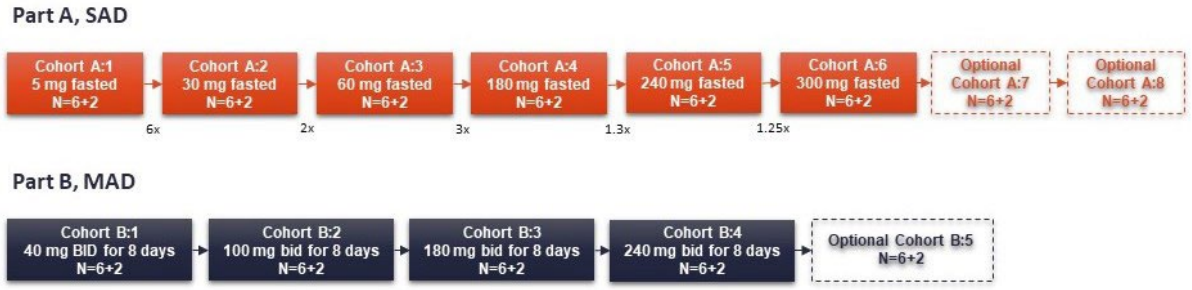
Part A, SAD including a food interaction cohort: safety, tolerability and PK in healthy males and healthy females of non-childbearing potential receiving single ascending doses of C106, see Section 8.1.1.

Part B, MAD: safety, tolerability and PK in healthy males and healthy females of non-childbearing potential receiving twice daily multiple ascending doses of C106 for 8 days, see Section 8.1.2.

Subjects included in the SAD part of the present study will not be included in the MAD part (regardless of whether 3 months have passed since the SAD participation).

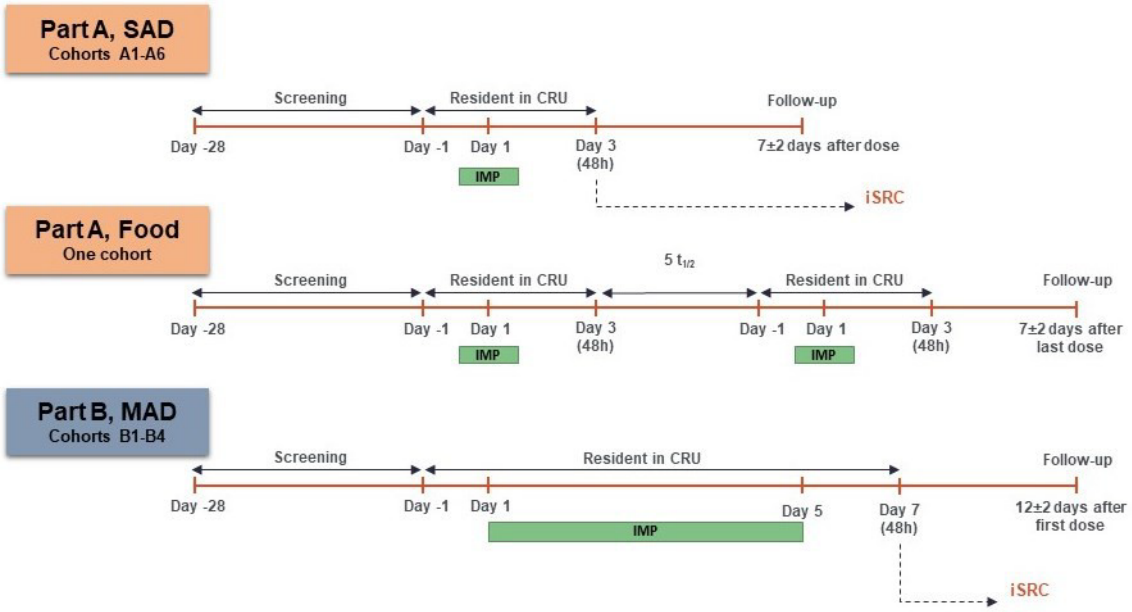
An overview of the planned cohorts and the trial design is shown in Figure 8.1-1 and Figure 8.1-2.

Figure 8.1-1 Overview of the planned cohorts



The actual doses given in Part A for cohorts 1 to 4 were 5, 30, 60 and 180 mg, corresponding to dose increment of 6, 2 and 3 times the previous dose. For cohort 5 and 6, the planned doses are 240 mg and 300 mg, corresponding to dose increments of 1.3 and 1.25 times the previous dose, respectively. The dose given in cohort 6 may be adjusted as recommended by the iSRC following evaluation of emerging safety, tolerability, and PK data in cohort 5. Cohorts A7, A8 and B5 are optional. The maximum oral dose in Part A and the maximum oral daily dose in Part B will not exceed 480 mg C106 (including the optional cohorts). The fed cohort is planned to be cohort A4. The first cohort in Part B (MAD) may be dosed after safety evaluation of the SAD cohort A3 if recommended by the iSRC. Each dose level in Part B will be selected such that the predicted maximum exposure will not exceed the maximum exposure (based on AUC and C_{max}) in previously evaluated SAD cohorts. Day 8: only morning dose (*i.e.*, in total 15 doses in Part B). The dosing frequency in Part B is planned to be BID but may be changed to QD if recommended by the iSRC.

Figure 8.1-2 Overview of the trial design



8.1.1 *Single Ascending Dose (SAD) part of the trial*

In Part A, single, oral doses of C106 will be administered in 6 sequential dose cohorts, each of 8 subjects. Within each cohort, subjects will be randomised to receive either C106 (n=6) or placebo (n=2) in the fasted state. The proposed doses are: 5, 30, 60, 180, 240 and 300 mg. The rationale for the starting dose and the planned dose escalation is detailed in Section 8.3. Up to 2 additional dose cohorts can be explored based on the safety, tolerability, and PK of the drug if recommended by the iSRC. The maximum oral dose in Part A will not exceed 480 mg C106.

Subjects will come for 3 visits to the Clinical Research Unit (CRU). Screening (Visit 1) will take place within 4 weeks of the planned dose (Day -28 to Day -1) and will include the subject's signing of the informed consent and an eligibility check, see Table 8.1-1. At Visit 2, subjects will reside at the CRU from Day -1 (the day before IMP administration) until Day 3 for single dose IMP administration, safety, tolerability, and PK assessments as outlined in Table 8.1-1 and detailed in Table 8.1-2. The subjects must fast for at least 10 hours before until 4 hours after the anticipated dosing time on Day 1. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 1 hour after dosing. The first 2 subjects in each cohort will be dosed in a sentinel fashion, 1 subject will receive C106 and the other will receive placebo as randomised. The subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals as detailed in Table 8.1-2. Ambulatory ECG telemetry will be used for cardiac surveillance up to 24 hours after IMP administration. There is immediate access to equipment, qualified staff, and an ICU in case of an acute emergency. To give sufficient time for observation of any reactions there will be at least 24 hours before dosing of the remaining 6 subjects, who will be dosed in groups of 3 subjects at least 24 hours apart. A final end-of-trial visit (Visit 3) will take place on Day 7 (±2 days) or after early withdrawal.

Cardiodynamic ECG assessments (collect and store) will be performed in all cohorts (except the first cohort A1) where C106 is given in the fasted state (*i.e.*, not in the fed period of the

fasted/fed cohort) and will include serial ECG extractions at baseline (prior to dosing) and at the same time points as PK sampling during the first 24 hours post-dose.

The doses given after the starting dose and time points for safety and PK sampling may be adjusted as recommended by the iSRC following evaluation of emerging safety, tolerability, and PK data. If needed, one visit for additional safety and PK assessments may be added based on recommendations from the iSRC.

Before initiating a new dose cohort, all subjects in the previous cohort must have been treated and all available safety, tolerability and plasma concentration data up until and including 48 hours post dose must have been evaluated by the iSRC, see Section 8.3.6. After collection of the last available 48-hour data, there will be at least one week between dose escalations. In case of dropouts, available data for the dropouts will be included in the iSRC evaluation. Based on emerging safety and PK data, the amount of required safety and PK data to be reviewed after a completed cohort might be adjusted.

Subjects are expected to participate in Part A for up to 37 days including a 28-day screening period. Subjects who are administered C106 both in the fasted and the fed state in Part A are expected to participate in the trial for up to 43 days + at least 5 half-lives of C106 (wash-out between fasting and fed IMP administrations).

The schedule of events for Part A is shown in Table 8.1-1 and detailed for Visit 2 in Table 8.1-2.

Trial assessments are described in Section 11.

8.1.1.1 Food interaction

One dose cohort (planned to be cohort A4) will be selected to investigate any potential food interaction. The predicted maximum exposure (taking into account a possible food interaction effect on the exposure) of the chosen dose level will not exceed the exposure tolerated in previously evaluated cohorts.

Subjects in the selected cohort will return to the clinic after a wash-out period of at least 5 half-lives (as determined by evaluation of PK data) to receive a second dose of C106 or placebo under fed conditions. In case of dropouts at the selected dose level, subjects may be replaced to guarantee a full cohort size for the food-interaction part of the trial (if considered necessary). Any replacers will receive active treatment. The assessments during fed conditions will be the same as during fasting conditions except that the subjects will consume an FDA recommended high-fat, high calorie breakfast 30 minutes prior to IMP administration as detailed in Section 10.5.1 and no screening visit will be conducted. Potential replacement subjects will come for a screening visit and perform one fasting cohort and one fed cohort.

The schedule of events for Part A is shown in Table 8.1-1 and detailed for Visit 2 in Table 8.1-2.

Trial assessments are described in Section 11.

Table 8.1-1 Schedule of events, Part A (SAD)

		Screening	**Trial intervention and observation period**				**Follow-up/End-of-trial**
Visit	**Refer to CTP section:**	**Visit 1**	**Visit 2[1,2]**				**Visit 3**
Assessment		Day -28 to Day -1	Admission Day -1	Day 1	Day 2	Day 3	Day 7 (±2)[3]
Informed Consent	14.3	X					
Inclusion/exclusion criteria	9.4, 9.5	X		X			
Demographics	11.2	X					
Medical/surgical history	11.2.5	X					
HIV, hepatitis B and C	11.2.7	X					
Alcohol test	11.2.9	X	X				
Weight/height (BMI)	11.2.4	X					
Serum FSH[4]	11.3.5	X					
Urine Drug Screen[5]	11.2.8	X	X				
Physical Examination	11.3.2	X		X[6]			X
Clinical Laboratory Profile[7]	11.3.5	X	X		X	X	X
Safety urine sampling	11.3.5	X	X		X	X	X
Urinalysis (dipstick)	11.3.5	X	X				X
Vital Signs[8]	11.3.4	X	X	X	X	X	X
12-lead safety ECG	11.3.2	X		X	X	X	X
Telemetry	11.3.3			X[9]			
Randomisation				X			
IMP administration	10.5			X[11]			
Cardiodynamic ECG[10]	11.5.3			X	X		
PK blood sampling	11.4.1			X	X	X	
PK urine sampling	11.4.2			X	X	X	
Breakfast					X	X	
High-fat breakfast[11]	10.5.1			X[11]			
Meals[12]			X	X	X	X	
Adverse events	11.3.1	------X------					
Prior and concomitant medications	11.2.6	------X------					

BMI=Body mass index. CTP=Clinical trial protocol. ECG=Electrocardiogram. FSH=Follicle stimulating hormone. HIV=Human immunodeficiency virus.

1. Details in separate flow chart (Table 8.1-2).
2. For the food-effect cohort, each subject will participate in 2 trial intervention and observation periods separated by a washout period.
3. Or after early withdrawal.
4. Females only (questionable cases).
5. Drug tests may also be performed at 1 to 2 additional random occasions during the trial.
6. Symptom driven physical examination.

7. Clinical chemistry, haematology and coagulation, see Section 11.3.5.
8. Systolic and diastolic blood pressure, pulse, respiratory rate at all visits indicated. Temperature will be measured on Day -1 only (other visits if indicated). For details regarding vital signs, see Section 11.3.4.
9. Ambulatory telemetry starting 30 min (±10 min) pre-dose and ending 24 hours (±20 min) post-dose.
10. Cardiodynamic ECG (collect and store) from cohort A2 (*i.e.*, not in cohort A1) and not in the fed part in the food effect cohort.
11. High-fat breakfast only for subjects participating in the fed part in the food effect cohort, see Section 10.5.1.
12. Day -1 Optional evening snack. Day 1: standardised lunch (at least 4 hours post-dose), optional snack, dinner and optional evening snack Day 2: non-standardised breakfast lunch, optional snack, dinner and optional evening snack. Day 3: non-standardised breakfast. For timing of meals, refer to Table 8.1-2.

Table 8.1-2 Detailed schedule of events, Part A (SAD) Day -1 to Day 2

	Day -1	Day 1													Day 2	Day 3
Assessment/time-point (hh:mm)	**Admission**	**Pre-dose**	**00:00**	**00:20**	**00:40**	**01:00**	**01:30**	**02:00**	**03:00**	**04:00**	**06:00**	**08:00**	**10:00**	**16:00**	**24 h**	**48 h**
Inclusion/exclusion criteria		X														
Urine drug screen	X															
Alcohol test	X															
Physical examination		X														
Clinical Laboratory profile	X														X	X
Safety urine sampling	X														X	X
Urinalysis (dipstick)	X															
Vital signs[1]	X	X			X			X		X	X		X		X	X
12-lead safety ECG		X			X			X		X	X		X		X	X
Telemetry[2]		------X------														
Randomisation		X														
IMP administration			X													
Cardiodynamic ECG[3]		------X------														
PK blood sampling		X		X	X	X	X	X	X	X	X	X	X	X	X	X
PK urine sampling[4]		X	------X[4]------													
Breakfast[5]															X	X
High-fat breakfast[6]		X														
Meals[7]	------X------															
Adverse events	------X------															
Prior and concomitant medications	------X------															

1. Systolic and diastolic blood pressure, pulse, respiratory rate at all time points indicated. Temperature will be measured on Day -1 only (other visits if indicated). For details regarding vital signs, see Section 11.3.4.
2. Telemetry: starting 30 min (±10 min) pre-dose and ending 24 hours (±20 min) post-dose.
3. A continuous ECG recording will be performed for 25 hours, starting 1 hour pre-dose on Day 1, in all cohorts in which subjects receive C106 or placebo in the fasted state, except for cohort A1. 12-lead ECGs will be extracted at 3 time points within one hour prior to dosing (at -45, -30 and -15 minutes) and subsequently at the same time points as PK blood draws up until and including 24-hours post-dose. Subjects will be supinely resting for at least 15 minutes before and 5 minutes after each time point. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures will be carried out in the order outlined in Section 11.1.
4. PK urine sampling: pre-dose (blank), 0-6 hours, 6-12 hours, 12-24 hours and 24–48 hours post-dose. No urine sampling in the food interaction cohort.
5. Fasting on Day 1. Breakfast on Day 2 and Day 3 after PK blood sampling.
6. High-fat breakfast only for subjects in the fed part in the food effect cohort, see Section 10.5.1. Following an overnight fast of at least 10 hours, subjects should start the meal 30 minutes prior to administration of the IMP and eat the meal in 30 minutes or less.
7. Day -1: Optional evening snack. Day 1: No breakfast. Standardised lunch at least 4 hours post dose. Standardised snack, dinner and optional evening snack at approximately 7 and 9 and 11 h post-dose. Day 2: Non-standardised breakfast after 24-hour PK sampling, lunch, snack, dinner and evening snack at approximately 4, 7 and 9 and 11 h post breakfast. Day 3: Non-standardised breakfast only.

8.1.2 *Multiple Ascending Dose (MAD) part of the trial*

In Part B, repeated, oral doses of C106 will be administered in 4 sequential dose cohorts. Within each cohort, subjects will be randomised to receive C106 (n=6) or placebo (n=2). The initial dose, dose escalations, and dosing schedule will be based on emerging safety, tolerability, and PK data observed in the SAD part of the trial (Part A) and on emerging data from the MAD part. Each dose level during the Part B will be selected such that the predicted maximum exposure will not exceed the maximum exposure (based on AUC and C_{max}) in previously evaluated SAD cohorts. The proposed doses are 40, 100, 180 and 240 mg BID. Twice daily dosing for 8 days is planned. Based on emerging PK data, once daily (QD) dosing may be applied if recommended by the iSRC. The number of dosing days may also be changed based on PK data from Part A (SAD), with the aim to reach steady state during the dosing period. The treatment duration will, however, not exceed the treatment duration in pre-clinical toxicology studies *i.e.*, 28 days. One additional dose cohort can be explored based on emerging safety, tolerability, and PK of the drug, if recommended by the iSRC. The maximum oral daily dose in Part B will not exceed 480 mg C106.

Subjects will come for 3 visits to the CRU. Screening (Visit 1) will take place within 4 weeks of the first dose (Day -28 to Day -1) and will include the subject's signing of the informed consent and an eligibility check, see Table 8.1-3 for details. At Visit 2, subjects will reside at the CRU from Day -1 (the day before IMP administration) until Day 10 for 8 days multiple dose IMP administration, safety, tolerability and PK assessments, see Table 8.1-3, Table 8.1-4 (Day -1 to Day) and Table 8.1-5 (Day 8 to Day 10). Subjects must fast from 2 hours prior to each IMP administration until 1 hour after. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 1 hour after dosing. On Day 8, only the morning dose will be administered (*i.e.*, in total 15 doses are planned).

The first 2 subjects in each cohort will be dosed in a sentinel fashion, 1 subject will receive C106 and the other will receive placebo as randomised. The subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals. There is immediate access to equipment, qualified staff and an ICU in case of an acute emergency. To give sufficient time for observation of any reactions there will be at least 24 hours before dosing of the remaining 6 subjects, who will be dosed in groups of 3 subjects at least 24 hours apart. A final end-of-trial visit (Visit 3) will take place on Day 22 (±2 days) or after early withdrawal.

For subjects participating in cohort B4, an assessment of endothelial function using EndoPAT will be performed before the first IMP administration (on Day -1 or 1), and 30±10 minutes after IMP administration on Day 7 (morning or evening). The EndoPAT assessments should be done at approximately the same time of the day on both occasions. Subjects must fast for at least 4 hours prior to the EndoPAT assessment until end of assessment. During fasting, water, but no other drinks, is allowed as desired. No drinks are allowed for 1 hour before and 1 hour after dosing.

Besides the starting dose and subsequent doses, also time points for safety and PK sampling may be adjusted as recommended by the iSRC following evaluation of emerging safety, tolerability, and PK data. If needed, one visit for additional safety and PK assessments may be added based on recommendations from the iSRC.

After collection of the last available 10 days data (48 hours after the last dose), there will be at least 2 weeks between dose escalations. Before initiating a new dose cohort, all subjects in the

previous cohort must have been treated and all available safety, tolerability and plasma concentration data up until and including 48 hours post last dose must have been evaluated by the iSRC. In case of non-replaced dosed dropouts, available data for the dropouts will be included in the iSRC evaluation. In case of dropouts, the iSRC may recommend including replacers to be able to make an informed recommendation on the next dose level. Based on emerging safety and PK data, the amount of required safety and PK data to be reviewed after a completed cohort might be adjusted.

Subjects are expected to participate in Part B for up to 47 days including a 28-day screening period.

The schedule of events for Part B is shown in Table 8.1-3 and is detailed for Visit 2 in Table 8.1-4 (Day -1 to Day 7) and Table 8.1-5 (Day 8 to Day 10).

Trial assessments are described in Section 11.

Table 8.1-3 Schedule of events, Part B (MAD)

	Screening	**Trial intervention and observation period**						**Follow-up/End-of-trial**
Visit	**Visit 1**	**Visit 2[1,2]**						**Visit 3**
Assessment/time-point	Day -28 to Day -1	Admission Day -1	Day 1	Days 2-7	Day 8	Day 9	Day 10	Day 22 (±2 days)[3]
Informed Consent	X							
Inclusion/exclusion criteria	X		X					
Demographics	X							
Medical/surgical history	X							
HIV, hepatitis B and C	X							
Alcohol test	X	X						
Weight/height (BMI)	X							
Serum FSH[4]	X							
Urine Drug Screen[4]	X	X						
Physical Examination	X		X[6]					X
Clinical Laboratory Profile[7]	X	X		X	X		X	X
Safety urine sampling	X	X		X	X		X	X
Urinalysis (dipstick)	X	X			X			X
Vital Signs[8]	X	X	X	X	X	X	X	X
12-lead ECG	X		X	X	X	X	X	X
Randomisation			X					
IMP administration			X	X	X			
Blood sampling for PK and metabolite profiling[9]			X	X	X	X	X	
Urine sampling for PK and metabolite profiling[9]			X		X			
PD (EndoPAT) assessment[10]			X	X				
Meals[11]		X	X	X	X	X	X	
Adverse events	------X------							
Prior and concomitant medications	------X------							

BMI=Body mass index. CTP=Clinical trial protocol. ECG=Electrocardiogram. FSH=Follicle stimulating hormone.

1. Details in separate flow charts (Table 8.1-4 and Table 8.1-5).
2. The duration of the intervention and observation period in Part B may be adjusted (8 days BID dosing duration assumed).
3. Or after early withdrawal.

4. Females only (questionable cases).
5. Drug tests may also be performed at 1 to 2 additional random occasions during the trial.
6. Symptom driven physical examination
7. Clinical chemistry, haematology and coagulation, see Section 11.3.5.
8. Systolic and diastolic blood pressure, pulse, respiratory rate at all visits indicated. Temperature will be measured on Day -1 only (other visits if indicated). For details regarding vital signs, see Section 11.3.4.
9. Metabolite profiling in plasma and urine at steady state only (Day 8 to Day 10).
10. Cohort B4 only. The EndoPAT assessment will be performed before the first IMP administration (Day -1 or Day 1) and 30±10 minutes after IMP administration on Day 7 (morning or evening dose). Subjects must fast for at least 4 hours prior to the EndoPAT assessment until end of assessment.
11. Breakfast at least 1-hour post-dose. Day -1 to Day 1 and Day 7 to Day 8: Standardised breakfast, lunch, snack, dinner and optional evening snack as applicable. Non-standardised meals Day 2, 3, 4, 5, 6, 9 and 10. For timing of meals, refer to Table 8.1-4 and Table 8.1-5.

Table 8.1-4 Detailed schedule of events, Part B (MAD) Day -1 to Day 7

Day	**Day -1**	**Day 1**													**Day 2**		**Day 3**		**Days 4 to 7**	
Assessment/time-point (hh:mm)	**Ad-mission**	**Pre-dose**	**00:00**	**00:20**	**00:40**	**01:00**	**01:30**	**02:00**	**03:00**	**04:00**	**06:00**	**08:00**	**10:00**	**12:00**	**24 h**	**36 h**	**48 h**	**60 h**	**D4: 72 h D5: 96h D6:120 h D7:144h**	**D4:84h D5: 108h D6:132 h D7: 156 h**
Inclusion/ exclusion criteria	X	X																		
Urine drug screen	X																			
Alcohol test	X																			
Physical examination		X[1]																		
Clinical laboratory. Profile	X																X[2]		X[2]	
Safety urine sampling	X																X[3]		X[3]	
Urinalysis (dipstick)	X																			
Vital signs[4]	X	X			X			X		X	X		X		X[5]		X[5]		X[5]	
12-lead ECG		X			X			X		X	X		X		X[5]		X[5]		X[5]	
Randomisation		X																		
IMP administration			X											X	X	X	X	X	X	X
Blood sampling for PK		X		X	X	X	X	X	X	X	X	X	X	X[6]	X[6]		X[6]		X[6]	
Urine sampling for PK[7]		X	------X[7]------																	
PD (EndoPAT) assessment[8]		X																	X	
Meals[9]	X																			

Adverse events	------X------
Prior and concomitant meds.	------X------

1. Symptom driven physical examination.
2. Clinical laboratory profile Day 3: pre-dose and Day 6: pre-dose.
3. Safety urine sampling Day 3 pre-dose and Day 6 pre-dose.
4. Systolic and diastolic blood pressure, pulse, respiratory rate at all time points indicated. Temperature will be measured on Day -1 only (other visits if indicated). For details regarding vital signs, see Section 11.3.4.
5. Vital signs and ECG Day 2 to Day 7: both in association with the morning dose and the evening dose, pre-dose and 1-hour post-dose.
6. Day 1: pre-dose at 12 hours. Day 2: pre-dose at 24 hours. Day 3 to Day 7: trough concentration (C_{trough}) pre-morning dose samples, see Section 11.4.1.
7. PK urine sampling pre-dose and 0-12 hours post-dose.
8. Cohort B4 only. The EndoPAT assessment will be performed before the first IMP administration (Day -1 or Day 1) and 30±10 minutes after IMP administration on Day 7 (morning or evening dose). Subjects must fast for at least 4 hours prior to the EndoPAT assessment until end of assessment.
9. Standardised meals on Day -1, Day 1, Day 7 and Day 8, non-standardised meals on Day 2 to Day 6. Breakfast at least 1 hour post dose, lunch, snack, dinner and optional evening snack at approximately 4, 7 and 9 and 10 h post-dose. Optional evening snack at least 2 hours before or 1 hour after IMP administration.

Table 8.1-5 Detailed schedule of events Part B (MAD) Day 8 to Day 10

Day	**Day 8**														**Day 9**	**Day 10**
Assessment/time-point (hh:mm)	**Pre-dose**	**00:00**	**00:20**	**00:40**	**01:00**	**01:30**	**02:00**	**03:00**	**04:00**	**06:00**	**08:00**	**10:00**	**12:00**	**16:00**	**24 h post last dose**	**48 h post last dose**
Clinical Laboratory profile	X															X
Safety urine sampling	X															X
Urinalysis (dipstick)	X															
Vital signs	X			X			X		X	X		X			X	X
12-lead ECG	X			X			X		X	X		X			X	X
IMP administration		X														
Blood sampling for PK and metabolite profiling	X[1]		X	X	X	X	X	X	X	X	X	X		X	X	X
Urine sampling for PK and metabolite profiling[2]		------X[2]-------														
Meals[3]	-------X------															
Adverse events	------X------															
Prior and concomitant medications.	------X------															

1. Trough (pre-dose) sample on Day 8, see Section 11.4.1.
2. PK urine sampling 0-12 hours post last dose (*i.e.*, morning dose Day 8).
3. Day 8: Standardised breakfast at least 1 hour post dose on Day 8, standardised lunch, snack, dinner and optional evening snack at approximately 4, 7 and 9- and 11-hours post-dose. Day 9: Non-standardised breakfast after PK sampling. Lunch, snack, dinner and optional evening snack at approximately 4, 7 and 9 and 11 h post-dose. Day 10: Breakfast only.

8.2 Rationale for trial design

The EMA guideline on strategies to identify and mitigate risks for FIH and early clinical trials with IMPs (EMEA/CHMP/SWP/28367/07 Rev. 1) has been considered.

The design of the trial is based on the aim to study safety, tolerability, and PK (including influence of food) of selected doses of C106 in a limited number of healthy volunteers. The design is adaptive, to allow for *e.g.*, flexible dose escalation and involves careful monitoring of the subjects' well-being. The time points for PK blood sampling are selected based on data obtained from previous non-clinical studies.

A placebo control will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active treatment.

Randomisation will be used to minimise bias in the assignment of subjects to dose groups and to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

For both Part A (SAD) and Part B (MAD) of the trial, a sequential-cohort, sentinel-dosing, ascending-dose design has been chosen for safety reasons as C106 is in early stage of clinical development, with Part A of the trial being the first time C106 will be administered to humans. Conducting the initial SAD and MAD trial with C106 in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

Oral administration has been chosen for all parts of the trial, as this is the intended clinical route of administration.

A 2-part cross-over design has been chosen for the food-effect evaluation, as a within-subject assessment of the influence of food on the PK of C106 increases the power for the given number of subjects.

An exploratory PD assessment will be performed in Part B (MAD), cohort B4 to investigate the effect of C106 on endothelial function. This data may support future trials on IPF-associated vasculopathy and further use of this PD assessment in early clinical development programs.

Overall, the trial will provide important data to support the design of further studies, both in healthy volunteers and in patients.

8.3 Selection of starting dose and rationale for planned dose escalation

8.3.1 *Selection of starting dose and rationale for dose escalation in Part A for cohorts 1 to 4 (completed)*

The starting dose in the single dose escalation (Part A) in this FIH trial was assessed based on the Maximum Recommended Starting Dose (MRSD) as well as the anticipated Minimal Anticipated Biological Effect Level (MABEL) approach.

The MRSD is based on the NOAEL derived from the 28-days repeat dose GLP toxicology studies in rat and dog. The NOAEL was determined to 15 (female)/10 (male) mg/kg and 20 mg/kg in dog. Human equivalent doses (HED) from the rat and dog data were estimated to 2.4 and 1.6 mg/kg based on the NOAEL in female and male rats, respectively, and 10.8 mg/kg

based on the NOAEL in dogs using allometric scaling. Applying a 10-fold safety margin to the HEDs, the MRSD based on the most sensitive species (male rat) is **9.7 mg** for a 60 kg person. If applying a 10-fold safety margin to the HEDs, the MRSD based on the dog is **65 mg** for a 60 kg person.

The starting dose was also assessed based on the MABEL. An approach of assuming the concentration leading to 15% receptor ligation in receptor binding assay was used to estimate the MABEL. A concentration of 1 nM C106 resulted in a 15% inhibition of the human AT_2R expressed in HEK-293 cells. Therefore, the MABEL for C106 (bound + unbound) assuming a 0.4% unbound fraction, is estimated to 122.4 ng/mL (1 nM *489.66 g/mol /0.004).

Estimation of human plasma clearance was conducted by an *in vitro-in vivo* extrapolation (IVIVE) approach using human liver hepatocyte stability data. Scaling of human hepatocyte intrinsic clearance (Cl_{int}) value of 4.0 µL/min/10^6 cells, according to the well-stirred model without correction for binding in plasma and incubations, resulted in an estimated human plasma clearance of 5.5 mL/min/kg. A starting dose of 5 mg, assuming 100% bioavailability and a plasma CL of 5.5 mL/min/kg, would result in a human plasma AUC_{inf} of 253 h*ng/mL for a 60 kg person. The estimated unbound human plasma AUC_{inf} following a 5 mg dose was 1.0 ng*h/mL (252* f_u=0.004).

Since C106 is an acidic molecule exhibiting high plasma protein binding, the distribution volume (V_{ss}) was assumed to be approximately 0.2 L/kg. Predictions of C_{max} following a 5 mg oral dose of C106 was based on a 1-compartmental model assuming 100% bioavailability, a plasma CL of 5.5 mL/min/kg, a V_{ss} of 0.2 L/kg, and an absorption rate constant (K_a) of 1 h^{-1}. The prediction, based on these assumptions, resulted in an C_{max} of 117 ng/mL. The estimated unbound human plasma C_{max} following a 5 mg dose was 0.47 ng/mL (117* f_u=0.004).

Based on the PK predictions and assuming maximum oral bioavailability, the dose of C106 expected to result in a transient minimal measurable pharmacological activity is **5.2 mg** (*i.e.*, the dose predicted to result in a C_{max} of 122.4 ng/mL).

The proposed starting dose of 5 mg was thus predicted to generate mean C_{max} and AUC_{inf} of 117 ng/mL and 253 ng*h/mL, respectively. These estimates provide a predicted safety margin of 19-fold when compared to the C_{max} (2190 ng/mL) and 56-fold when compared to the AUC_{last} (14200 ng*h/mL) at NOAEL in the most sensitive species (male rat), see Table 8.3-1.

When compared to the NOAEL of the most sensitive non-rodent species (female dog), these estimates provide a predicted safety margin of 75-fold when compared to the C_{max} (8730 ng/mL) and 63-fold when compared to the AUC_{last} (15900 ng*h/mL), see Table 8.3-1.

Table 8.3-1 Predicted human exposure at the starting dose and margins vs the NOAEL in rat and dog

Species	NOAEL (mg/kg)	Exposure at NOAEL (C_{max} ng/mL)	Exposure at NOAEL (AUC_{last} h*ng/mL)	C_{max}-based margin *vs.* NOAEL	AUC-based margin *vs.* NOAEL
Rat, males	10	Tot: 2190 Unbound*: 4.4	Total: 14200 Unbound*: 28.4	Total: 19 Unbound*: 9	Total: 56 Unbound*: 28
Rat, females	15	Total: 2880 Unbound*: 5.8	Total: 29300 Unbound*: 58.6	Total: 25 Unbound*: 12	Total: 116 Unbound*: 59
Dog, males	20	Total: 11000 Unbound*: 245	Total: 20500 Unbound*: 457	Total: 94 Unbound*: 522	Total: 81 Unbound*: 457
Dog, females	20	Total: 8730 Unbound*: 193	Total: 15900 Unbound*: 355	Total: 75 Unbound*: 414	Total: 63 Unbound*: 355
Human, predicted (5 mg)		Total: 117 Unbound*: 0.47	Total: 253 Unbound*: 1.0	NA	NA

* For plasma protein binding (PPB), see Section 6.1.4.

There exists a degree of uncertainty associated with the predictions of human C_{max} and AUC_{inf} for the proposed starting dose. However, the safety of activating the AT_2R has previously been evaluated with the AT_2R agonist C21 in 3 completed Phase 1 trials (C21-001-16, C21-002-16, and C21-003), in 1 completed Phase 2 trial in hospitalised patients with COVID-19 (VP-C21-006) and in 1 completed Phase 2 trial in patients with Raynaud's phenomenon secondary to SSc (VP-C21-004) with a total of 146 subjects exposed to at least one oral dose of C21 in these trials. C21 has a similar potency, selectivity and PPB as C106, and a similar PK profile in humans is anticipated. Across the trials, C21 has been well tolerated at single and daily oral doses up to 200 mg. Following single oral administration of 200 mg C21, the mean C_{max} was 4605 ng/mL and mean AUC_{inf} was 5619 ng*h/mL (C21-003).

The starting dose of **5 mg** was considered supported by both the estimated MRSD and MABEL. The selection of the starting dose was further supported by the clinical data with the analogue AT2R agonist C21, which has been shown to be well tolerated at single and daily oral doses of up to 200 mg.

The actual doses given in Part A for cohorts 1 to 4 were 5, 30, 60 and 180 mg, corresponding to dose increment of 6, 2 and 3 times the previous dose. For a summary of the observed exposures in cohorts 1 to 4, see Table 8.3-2. The plasma exposure of C106 was lower than expected at all dose cohorts evaluated and the doses in Part A were adjusted accordingly.

The start dose in Part A was selected assuming 100% oral bioavailability and linear pharmacokinetics up to 200 mg. In case the systemic exposure following the first cohort was appreciably smaller than predicted or below the lower limit of quantification (LLOQ), multiple, maximum 6-fold, dose escalations were allowed until the exposure is within the predicted range of the trial.

For further details on the prerequisites for the transition from single to multiple dosing, refer to Section 8.3.4.

8.3.2 *Selection of doses for cohorts 5 and 6 in Part A (SAD)*

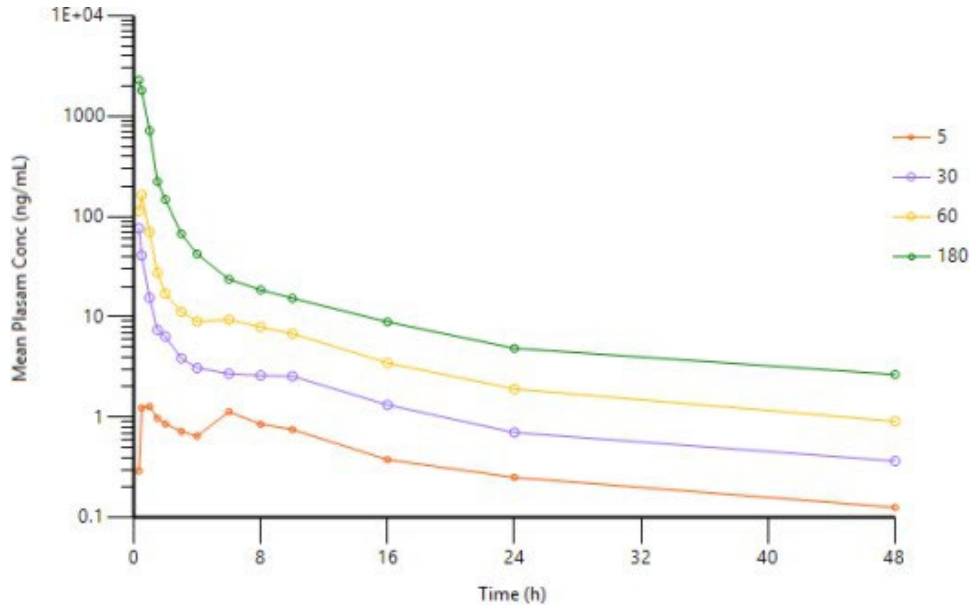
Based on the interim PK analysis of cohorts 1 to 4 (Table 8.3-2), the planned doses of C106 in cohorts 5 and 6 have been adjusted. The results from the interim PK analysis showed that the plasma exposure of C106 was lower than expected and that C106 exhibited a non-linear PK. The increase in mean C_{max} and AUC_{inf} for cohort A:4 (180 mg) in comparison to cohort A:3 (60 mg) was 13.2-fold and 7.2-fold, respectively (Table 8.3-2). C106 exhibited a fast absorption with a T_{max} of 20-40 minutes and the mean C_{max} and AUC_{inf} were 2590 ng/mL and 2244 h*ng/mL, respectively, with a mean $T_{1/2}$ of approximately 11 hours (Figure 8.3-1). The mean margin to the exposure stopping criteria for Part A cohort 4 was at least 3.4-fold for C_{max}.

For cohorts 5 and 6, the planned doses are 240 mg and 300 mg, corresponding to dose increments of 1.3 and 1.25 times the previous dose, respectively. The dose given in cohort 6 may be adjusted as recommended by the iSRC following evaluation of emerging safety, tolerability, and PK data in cohort 5. Up to 2 additional dose cohorts can be explored based on the safety, tolerability, and PK of the drug, if recommended by the iSRC. The iSRC recommendation, as well as Sponsor's decision, will be documented in a non-substantial amendment to the clinical trial protocol (CTP). For dose escalation and stopping rules in Part A, refer to Table 8.3-3.

Table 8.3-2 Observed exposure in humans and margin to stopping criteria

Cohort	***Dose (mg)***	***N***	***Observed C_{max} (ng/mL) Mean (Max)***	***Observed AUC_{inf} (h*ng/mL) Mean (Max)***	***Stopping criteria***		***Margins C_{max} Mean***	***Margins AUC Mean***
					C_{max} (ng/mL)	***AUC (h*ng/mL)***		
Cohort A:1	5	6	1.65 (2.85)	20.7 (35.0)	8730	15900	5300	770
Cohort A:2	30	6	82.3 (156)	114 (142)	8730	15900	106	139
Cohort A:3	60	6	196 (278)	312 (501)	8730	15900	44.5	51.0
Cohort A:4	180	6	2590 (5130)	2244 (3280)	8730	15900	3.4	7.1

Figure 8.3-1 Pharmacokinetic mean concentrations for conducted SAD cohorts– logarithmic scale C106 (ng/mL)



8.3.3 *Maximum exposure and dose*

As discussed in detail in Section 6.3, there is considerable evidence in the literature that the infiltration of inflammatory cells in some organs in rats (critical finding for setting the NOAEL in rats) is species specific and of no human relevance. This suggest that the exposures at NOAEL in dogs are more relevant to set a human exposure limit than the NOAEL in rats.

The highest dose of C106 to be tested in this trial (Part A or Part B) shall, thus, not surpass the exposure at NOAEL in the female dog, *i.e.*, a mean value of **8730 ng/mL** and **15900 ng*h/mL** for C_{max} and AUC_{last}, respectively, see Table 8.3-1.

The maximum oral dose in Part A and the maximum oral daily dose in Part B will not exceed 480 mg C106.

8.3.4 *From single to multiple dosing and rationale for dose escalation Part B*

Following completion of cohort A3 of Part A (SAD), the iSRC will evaluate all available safety, tolerability, and PK data up until and including at least 48-hour data from SAD cohort A3 and, if necessary, suggest adjustments to dose levels, dosing regimens or dosing duration for Part B (MAD) in a written recommendation to the Sponsor. If no safety or tolerability concerns have been identified, cohort B1 of Part B (MAD) can be initiated approximately in parallel with cohort A4 of Part A (SAD), as decided by the Sponsor.

In Part B, the initial dose, dose escalations and dosing schedule will be based on emerging safety, tolerability, and PK data observed in the SAD part of the trial (Part A) and on emerging data from the MAD part.

The planned dose escalation steps are 40 mg BID, 100 mg BID, 180 mg BID and 240 mg BID. In Part B, the dose increments between the dose cohorts will be no more than 3-fold.

Each dose level during Part B will be selected such that the predicted steady state AUC_{tau} and C_{max} will not exceed the maximum exposure (based on AUC_{inf} and C_{max}) in previously evaluated SAD cohorts.

8.3.5 *Stopping criteria for dose escalation*

The Principal Investigator and the iSRC (Section 8.3.6) will follow the recommendations and grading system of CTCAE v5.0 [40], see Section 11.3.1.7 but also take into account the recommendations published by Sibille *et al.* 2010 [41], which is an adaptation to FIH studies of the grading systems previously proposed by National Cancer Institute (NCI) [1], World Health Organisation (WHO) [42], National Institute of Health (NIH) [43] and the US Food and Drug Administration (FDA) [44]. The grade, the frequency of AEs and the blindness will be considered.

A rolling review of emerging safety data will be performed throughout the trial taking into account any AEs, the number of subjects in whom they occur, concurrency of more than one event within the same subject and any trends. Changes from baseline measurements will also be considered and not just absolute cut-off based on upper- or lower limits of normal that might apply for healthy volunteers.

Trends or safety signals, which are not necessarily covered by the stopping criteria in Table 8.3-3 and Table 8.3-4 may warrant the scheduling of *ad hoc* iSRC meetings after which the iSRC will make recommendations to the Sponsor on e.g. whether to terminate the trial or to stop dosing in individual subjects or a certain cohort.

Additional withdrawal criteria are summarised in Section 9.8.

Table 8.3-3 Dose escalation and stopping rules in Part A (SAD)

	Stop criterion	Action taken
	At individual and dose group level	
1	If 1 on active treatment subject has an SAE assessed as related to IMP administration	1. Stop dosing of subject with a potential serious adverse reaction (SAR). Await dosing of additional subjects until the iSRC's recommendation and the Sponsor's decision on continuation. 2. Unblinding of subject with potential SAR. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Sponsor decides how to proceed: The subject received active treatment, i.e., met stopping criterion: stop further dosing at this dose level for all subjects. Sponsor decides if the trial will be terminated or if dosing will resume at a lower dose level.
2	If 2 subjects on active treatment in the same cohort have severe, non-serious AEs assessed as related to the IMP administration (independent of within or not within the same System organ class [SOC]).	1. Stop dosing of subjects with severe, non-serious potential adverse reactions. Await dosing of additional subjects until the iSRC's recommendation and the Sponsor's decision on continuation. 2. Unblinding of the subjects with potential adverse reactions. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Sponsor decides how to proceed: Both subjects received active treatment, i.e., met stopping criterion: stop further dosing at this dose level for all subjects. Sponsor decides if the trial will be terminated or if dosing will resume at a lower dose level.
3	If the next planned dose level is predicted to result in an exposure exceeding either an AUC_{inf} of 15 900 ng*h/mL or a C_{max} of 8730 ng/mL based on the NOAEL in the most sensitive non-rodent species (female dog).[1]	1. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 2. Sponsor decides if the trial will be terminated or if dosing in the next cohort will resume at a lower dose level.
	Final dosing stop and termination of trial	
4	If 2 subjects on active treatment in different cohorts have SAEs assessed as related to IMP administration	1. Stop dosing of subjects with potential SAR. Withdrawal of subjects. 2. Unblinding of subjects with potential SARs. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Sponsor decides how to proceed Both subjects received active treatment, *i.e.,* met stop criterion: Termination of trial. One subject (1) received active treatment, *i.e.*, met stop criterion: See stop criterion no. 1.

1. When reviewing emerging data in relation to this criterion, the maximum exposure observed in individual subjects within a cohort rather than the mean exposure should be taken into account. The exposure predictions are normally based on the highest observed C_{max} and AUC_{inf}/AUC_{tau} in the previous conducted SAD cohort assuming linear kinetics. If non-linear PK is observed in previously conducted cohorts, this will also be considered.

Table 8.3-4 Dose escalation and stopping rules in Part B (MAD)

Stop criterion	Action taken
At individual and dose group level	
If 1 subject on active treatment has an SAE assessed as related to IMP administration	1. Stop dosing of subject with a potential serious adverse reaction (SAR). Await dosing of additional subjects until the iSRC's recommendation and the Sponsor's decision on continuation. 2. Unblinding of subject with potential SAR. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Sponsor decides how to proceed: The subject received active treatment, i.e., met stopping criterion: stop further dosing at this dose level for all subjects. Sponsor decides if the trial will be terminated or if dosing will resume at a lower dose level.
If 2 subjects on active treatment in the same cohort have severe, non-serious AEs assessed as related to the IMP administration (independent of within or not within the same System organ class [SOC])	1. Stop dosing of subjects with severe, non-serious potential adverse reactions. Await dosing of additional subjects until the iSRC's recommendation and the Sponsor's decision on continuation. 2. Unblinding of the subjects with potential adverse reactions. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Sponsor decides how to proceed: Both subjects received active treatment, i.e., met stopping criterion: stop further dosing at this dose level for all subjects. Sponsor decides if the trial will be terminated or if dosing will resume at a lower dose level.
If 2 subjects on active treatment in the same cohort have a grade 2 hair loss (≥50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact) assessed as related to the IMP administration.	1. Stop dosing of subjects with hair loss. Await dosing of additional subjects until the iSRC's recommendation and the Sponsor's decision on continuation. 2. Unblinding of the subjects with potential adverse reactions. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Sponsor decides how to proceed. Both subjects received active treatment, i.e., met stopping criterion: stop further dosing at this dose level for all subjects. Sponsor decides if the trial will be terminated or if dosing will resume at a lower dose level.
If the next planned dose level is predicted to result in an exposure exceeding either an AUC_{0-24} of 15 900 ng*h/mL or a C_{max} of 8730 ng/mL based on the NOAEL in the most sensitive non-rodent species (female dog).[1]	1. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 2. Sponsor decides if the trial will be terminated or if dosing in the next cohort should commence at a lower dose level than intended.
Final dosing stop and termination of trial	
If 2 subjects on active treatment in different cohorts have SAEs assessed as related to IMP administration	1. Stop dosing of subjects with potential SAR. Withdrawal of subjects. 2. Unblinding of subjects with potential SARs. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Subjects meet stop criterion: Termination of trial.

1. When reviewing emerging data in relation to this criterion, the maximum exposure observed in individual subjects within a cohort rather than the mean exposure should be taken into account. The exposure predictions are normally

based on the highest observed C_{max} and AUC_{inf}/AUC_{tau} in the previous conducted cohort assuming linear kinetics. If non-linear PK is observed in previously conducted cohorts, this will also be considered.

8.3.6 *Internal safety review committee*

Before initiating a new dose cohort, all subjects in the previous cohort must have been treated and all available safety, tolerability, and plasma concentration data up until and including 48 hours post dose (Part A, SAD) and 48 hours post last dose (Part B, MAD) must have been evaluated by the iSRC. After collection of the last available 48-hour data, there will be at least one week between dose escalations in Part A (SAD) and 2 weeks in Part B (MAD). Any indication of hair loss emerging after the 48-hour data cut off will be considered by the iSRC at the iSRC meeting. In case of dropouts, available data for the dropouts will be included in the iSRC evaluation. The iSRC may recommend including replacers (Part B, MAD) to be able to make an informed recommendation on the next dose level.

If C106 is considered safe and tolerable, the iSRC will provide the Sponsor with a written recommendation on the next dose level (Part A, SAD) or on the starting dose and subsequent dose levels (Part B, MAD) based on the predicted exposure.

Details regarding timing of iSRC review and the data to be reviewed will be provided in a separate iSRC charter. Based on emerging safety and PK information, the amount of safety and PK data to be reviewed after a completed cohort might be adjusted.

The voting members of the iSRC will consist of the Principal Investigator or delegate and the Sponsor's Medical Representative or delegate. In addition, the trial clinical research manager (CRM), the trial pharmacokineticist and additional Sponsor representatives will be invited as appropriate. Further internal or external experts may be invited and consulted by the iSRC as appropriate.

An adaptive dosing strategy will be applied to allow for a flexible and safe dose escalation. The planned dose escalation is outlined in Section 8.3. The actual doses given in each cohort will be guided by the iSRC recommendations based on available safety, tolerability and PK data. Every dose step is thus adjustable and the recommendation to the Sponsor may be to continue with a higher or lower dose than the intended dose, repeat the same dose level, continue with an intermediate dose level or to stop dosing. The maximal daily dose in the trial will not exceed 480 mg.

The recommendation of the iSRC on the next dose level will be taken in consensus between the iSRC members and documented as appropriate. In case there is disagreement between the 2 voting members, the most conservative approach will be taken. It is not acceptable to repeat a dose level where any of the dose escalation stopping rules have been met.

The duration of the residential periods in each part may be changed following review of data from earlier cohorts. An additional visit for safety and PK sampling may be added if considered necessary by the iSRC. Should the duration of any residential period change, subsequent changes to the timing of safety and PK assessments will be done as necessary. A significantly longer $T_{½}$ than expected may require a change in the dosing interval, *i.e.*, once daily dosing rather than twice daily as currently planned. Should the dosing interval change, subsequent changes to the timing of safety and PK assessments will be done as necessary. Two optional cohorts may be added in Part A (SAD) and 1 optional cohort may be added in Part B (MAD), if recommended by the iSRC. Such changes to the CTP will be documented in non-substantial amendments.

The treatment code may be broken by the iSRC during the assessment process (partial un-blinding) in accordance with stopping criteria described in Section 8.3.6. The medical staff and the subjects will still be blinded for the treatments (active drug or placebo) to be administered in the subsequent dose groups/cohorts in order to minimise bias. If unblinding was considered necessary, the iSRC meeting may consist of a closed part and an open part. Only voting members will be unblinded.

9 TRIAL POPULATION

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

9.1 Recruitment

The subjects will be recruited from CTC's database of healthy volunteers and patients, as well as from strategic marketing campaigns. Advertisements in social media and other media (newspapers, internet, radio, local distribution of flyers etc.) will be used to reach the target audience. The advertisement texts approved by the independent ethics committee (IEC) will be used to create all the digital, radio and print material for recruitment.

9.2 Screening and enrolment log

Investigators must keep a record of all screened subjects even if they were not subsequently included in the trial. This information is necessary to verify that subjects were selected without bias. The reason for screen failure should be stated for all subjects screened but not included. The reason for withdrawal should be stated for all subjects included but not completed.

A screening number will be allocated to each subject in connection to the informed consent process at the Screening visit. The screening number is generated automatically in the electronic case report form (eCRF). The screening number will allow identification of subjects irrespective of their possible eligibility for the trial.

Subjects included and randomised will be assigned a randomisation number (1101, 1102 etc. in Part A (SAD), cohort A1 and so on and 2101, 2102 etc. in Part B (MAD), cohort B1 and so on). The first digit will correspond to the trial part, the second digit will correspond to the cohort and the 3rd and 4th digits correspond to the subject number.

If a subject cannot receive the planned dose of IMP within 28 days after screening (*i.e.*, the time interval between signing informed consent until dose administration) the subject should be rescreened before proceeding in the trial.

9.3 Number of subjects

Approximately 160 subjects will be screened (approximately 96 for Part A and 64 for Part B) to achieve a total of 80 randomised and dosed subjects. The number may increase if additional dose cohorts need to be investigated and/or if recommended by the iSRC.

Part A: 48 subjects will be randomised and dosed in 6 cohorts (Cohorts A1 to A6, each of 8 subjects with 6 subjects receiving C106 and 2 subjects receiving placebo).

Part B: 32 subjects will be randomised and dosed in 4 cohorts (Cohorts B1 to B4, each of 8 subjects with 6 subjects receiving C106 and 2 subjects receiving placebo).

If indicated by emerging data and recommended by the iSRC, 2 cohorts (8+8 subjects) may be added to Part A and 1 cohort (8 subjects) may be added to Part B. In such cases, and to account for potential dropouts, additional subjects might be included in the trial.

For replacements of subjects who discontinue from the trial, see Section 9.8.

9.4 Inclusion criteria

For inclusion in the trial, subjects must fulfil the following criteria:

1. Willing and able to give written informed consent for participation in the trial. The signed informed consent should be obtained before initiation of any trial related procedures.
2. Healthy males and healthy females of non-childbearing potential aged 18-65 years inclusive.
3. Body Mass Index (BMI) ≥ 18.5 and ≤ 30.0 kg/m^2.
4. Clinically normal medical history, physical findings, vital signs, ECG, and laboratory values at the time of screening, as judged by the Investigator.
5. Women of non-childbearing potential, defined as pre-menopausal females who are sterilized (tubal ligation or permanent bilateral occlusion of fallopian tubes); or females who have undergone hysterectomy or bilateral oophorectomy; or post-menopausal defined as 12 months of amenorrhea (in questionable cases a blood sample with simultaneous detection of follicle stimulating hormone [FSH] ≥ 25 IU/L is confirmatory).

   Male subjects must be willing to use condom or be vasectomised or practice sexual abstinence to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after (last) dosing with the IMP. Their female partner of child-bearing potential must use highly effective contraceptive methods with a failure rate of < 1% to prevent pregnancy (combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD]or intrauterine hormone-releasing system [IUS]) from at least 4 weeks prior to dose to 3 months after last dose.

9.5 Exclusion criteria

Subjects must not enter the trial if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the trial, or influence the results or the subject's ability to participate in the trial.
2. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP.
3. Malignancy within the past 5 years except for in situ removal of basal cell carcinoma.
4. Any planned major surgery within the duration of the trial.
5. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and Human Immunodeficiency Virus (HIV).

6. After 10 minutes supine rest at the time of screening, any vital signs values outside the following ranges:
   - Systolic blood pressure <90 or >140 mmHg, or
   - Diastolic blood pressure <50 or >90 mmHg, or
   - Pulse <40 or >90 bpm
7. Prolonged QTcF (>450 ms), PR interval < 120 ms or > 240 ms, QRS>115 ms, clinically significant cardiac arrhythmias or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the Investigator.
8. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to C106.
9. Regular use of any prescribed or non-prescribed medication including antacids, analgesics, herbal remedies, vitamins and minerals within 2 weeks prior to the (first) administration of IMP, at the discretion of the Investigator.
10. Planned treatment or treatment with another investigational drug within 3 months prior to Day -1. Subjects consented and screened but not dosed in previous clinical trials are not excluded.
11. Current smokers or users of nicotine products. Irregular use of nicotine (*e.g.*, smoking, snuffing, chewing tobacco) less than three times per week is allowed before screening visit.
12. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to administration of the IMP.
13. History of alcohol abuse or excessive intake of alcohol, as judged by the Investigator.
14. Presence or history of drug abuse, as judged by the Investigator.
15. History of, or current use of, anabolic steroids.
16. Excessive caffeine consumption defined by a daily intake of >5 cups of caffeine containing beverages.
17. Plasma donation within one month of screening or blood donation (or corresponding blood loss) during the three months prior to screening.
18. Investigator considers the subject unlikely to comply with trial procedures, restrictions, and requirements.

9.6 Restrictions during the trial period

9.6.1 *General restrictions*

The subjects must be willing to comply to the below restrictions during the entire trial duration i.e., from screening to the end-of-trial visit (or longer if specified).

- Contraception Requirements: The male volunteers are expected to use condom to prevent pregnancy and drug exposure of a partners and refrain from donating sperm from the date of dosing until 3 months after last dosing of the IMP. Fertile female partners are expected to use highly effective contraceptive methods with a failure rate of

< 1% to prevent pregnancy from at least 4 weeks prior to dose to 3 months after last dose (for details regarding contraceptive methods, refer to inclusion criterion No 5).

- Meals and Dietary Restrictions: Standardised meals will be served on Day -1 and Day 1 in Part A (SAD) and on Day -1, Day 1, Day 7 and Day 8 in Part B (MAD). Non-standardised meals will be served on the other days. Lunch will be served at least 4 hours post-dose. Snack, dinner, and optional evening snack will be served approximately 7-, 9- and 11-hours post-dose, respectively.

  For details on IMP administration in fasted and fed state, refer to Section 10.5.1.

  Standardised meals: A menu option decided by CTC. The meal selection is standardised in the sense that the nutritional content of the meals should be similar at each time point of each treatment day.

- Fasting: In Part A (SAD), the subjects should be fasting overnight (10 hours) before Day 1 and until 4 hours post-dose (except in the fed cohort). In Part B (MAD), subjects must fast from 2 hours prior to each IMP administration until 1-hour post-dose. Water is allowed *ad libitum* at the clinic except 1 hour before dose and 1 hour after dose. The IMP will be taken with water (approximately 240 mL, including the volume of the IMP). Subjects participating in Part B, cohort B4 must fast for at least 4 hours prior to the EndoPAT assessment until end of assessment.

- Sun protection: Protection from the sun is required from each C106 administration until 3 days post dose in Part A and from the first until 3 days after the last C106 administration in Part B. Study subjects are required to follow the recommendations given by Centres for Disease Control and Prevention (CDC, see [45]):
  - Stay in the shade, especially during sun peak hours of 10 AM to 4 PM.
  - Wear clothing that covers arms and legs.
  - Use a hat or cap that shades the face, head, ears, and neck.
  - Wear sunglasses that block both ultraviolet A (UVA) and ultraviolet B (UVB) rays
  - Proper use of a broad-spectrum sunscreen with a sun protection factor (SPF) of 15 or higher.
  - Abstain from use of tanning beds.
- Alcohol: Consumption of alcohol is not allowed within 48 hours prior to the screening visit and all subsequent visits to the clinic including the end-of-trial visit of each part. In addition, consumption of alcohol is disallowed during all visits to the clinic.
- Drugs of abuse: Use of drugs of abuse is not allowed within 48 hours prior to the screening visit and during the entire trial duration *i.e.*, from screening to the end-of-trial visit.
- Coffee: Consumption of up to 5 cups of coffee per day will be allowed from screening to the end-of-trial visit of each part.
- Xanthine or taurine containing products/beverages: Energy drinks (*e.g.*, Red Bull) are not allowed from screening to the end-of-trial visit of each part.
- Nicotine: Smoking or use of nicotine-containing products is not allowed from screening to the end-of-trial visit of each part.

- Grapefruit and grapefruit containing products: Consumption of grapefruit and/or grapefruit containing products, Seville oranges is not allowed from screening to the end-of-trial visit of each part.
- Exercise: The subjects must refrain from strenuous exercise for 72 hours before and during any visit to the clinic.
- Blood donation: The subjects must not donate blood or plasma during the trial until 3 months after the final medical examination at the end-of-trial visit of each part.
- Participation in other clinical trials: The subjects are not allowed to participate in any other interventional clinical trial from screening to the end-of-trial visit of each part.
- Trial intervention and observation periods: The subjects are not allowed to leave the research clinic during residential stays at the research clinic (Visit 2 in both Part A and Part B), unless authorised by the trial personnel.

9.6.2 *Prior and concomitant therapy*

Prohibited medication

Regular use of any prescribed or non-prescribed medication including antacids, analgesics, herbal remedies, vitamin supplements and minerals from 2 weeks prior to the (first) administration of IMP at the discretion of the investigator.

Any use of prescribed or non-prescribed medication including antacids, analgesics, herbal remedies, vitamin supplements and minerals from the (first) administration of IMP until the end-of trial visit of each part is not allowed except as detailed below.

Allowed medication

- Paracetamol in doses up to 2000 mg/day for a maximum of 3 consecutive days. If this amount of paracetamol is not sufficient for treatment of the subjects, withdrawal should be considered.
- Nasal decongestants without cortisone, antihistamine or anticholinergics for a maximum of 10 days.
- Hormone replacement therapy.

Other medications considered necessary for the subject's safety and wellbeing may be given at the discretion of the Investigator during the residential period. Following consultation with the Sponsor, the Investigator will determine whether or not the subject should continue in the trial.

9.7 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not fulfil all eligibility criteria and are not subsequently randomised in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects. Minimal information includes documentation of signed and dated informed consent form (ICF) and reason(s) for screening failure.

Re-screening can be performed if any of the following were reasons for screening failure or non-randomisation (as judged by the Investigator):

- Practical reasons.
- Non-significant medical conditions (*e.g.,* influenza, nasopharyngitis).
- Reserve subject in previous cohort.
- Plasma or blood donation outside allowed time windows.

For subjects who are re-screened, a new screening number will be assigned and a new, signed ICF will be collected.

9.8 Subject withdrawal

9.8.1 *General withdrawal criteria*

Subjects are free to discontinue their participation in the trial at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care. If possible, the reason for withdrawal of consent should be documented.

Subjects may be withdrawn from the trial at any time at the discretion of the Investigator.

Reasons for withdrawal include:

- Subject decision
- Severe non-compliance to trial protocol procedures, as judged by the Investigator and/or Sponsor
- Subject is lost to follow-up
- Significant AEs posing a risk for the subject, as judged by the Investigator and/or Sponsor
- Withdrawal of informed consent to the use of biological samples
- Pregnancy
- Death
- Meeting of an exclusion criterion during the trial, which, in the opinion of the Investigator, may pose a risk for the subject
- Use of prohibited medication

9.8.2 *QTc withdrawal criteria*

A subject meeting the criteria below will be withdrawn from the trial. The same QT correction formula will be used to determine discontinuation throughout the trial.

- QTcF > 500 msec
- Change from baseline: QTcF > 60 ms

Withdrawal decisions will be based on an average QTc value of triplicate ECGs. If an ECG demonstrated a prolonged QT interval, two more ECGs will be obtained over a brief period

and the averaged QTc values of the three ECGs used to determine whether the subject should be discontinued from the trial.

9.8.3 *Liver chemistry withdrawal criteria*

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology. Trial treatment will be stopped for the individual subject if any of the following liver chemistry stopping criteria, defined in the FDA Guidance on Drug-Induced Liver Injury [46], is met:

- Alanine aminotransferase (ALT) 3 x Upper Limit of Normal (ULN) and total bilirubin ≥ 2xULN (>35% direct bilirubin); **or** ALT 3xULN and INR > 1.5.

NOTE: plasma bilirubin fractionation will be performed.

- ALT 5xULN.
- ALT 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia).

9.8.4 *Procedures for discontinuation of a subject from the trial*

A subject who prematurely discontinues participation in the trial will always be asked about the reason(s) for discontinuation and the presence of any AEs. If a subject withdraws consent, the Investigator must ask the subject if he/she is willing, as soon as possible, to be assessed according to the procedures scheduled for the end-of-trial visit in each part. Any ongoing AEs will be followed as described in Section 11.3.1.15.

The primary reason for discontinuation/early withdrawal must be specified in the eCRF and final drug accountability must be performed. If the primary reason is an AE, the AE must be specified.

9.8.5 *Subject replacement*

Subjects who are prematurely withdrawn from the trial for any reason except the occurrence of AEs assessed as possibly or probably related to trial treatment may be replaced during the course of the trial.

Part A (SAD): subjects who are randomised but not dosed will be replaced. Subjects who are dosed will not be replaced.

In the event of dropouts in the fed cohort, subjects may be replaced to guarantee a full cohort size for the food-interaction part of the trial. Any replacers will receive active treatment both in the fasted and fed state.

Part B (MAD): Subjects who are randomised but not dosed will be replaced. Subjects who were prematurely withdrawn from the trial for any reason except the occurrence of AEs assessed at least possibly related to the IMP may be replaced.

9.9 Randomisation

On Day 1 of each part, subjects in each cohort will be randomised to receive either C106 (n=6) or placebo (n=2). Subjects will be randomised in 2 blocks. The first 2 subjects in a cohort will be randomised to C106 (n=1) or placebo (n=1). The next subjects will be randomised in a 5:1 ratio to receive C106 (n=5) or placebo (n=1). A computer-generated randomisation list will be created using SAS Proc Plan, SAS Version 9.4. The randomisation list will contain subject number and treatment and will be kept by the randomiser in a sealed envelope until database lock. A copy of the randomisation list will be kept by an unblinded IMP preparation staff member at the site.

Sealed individual, treatment code envelopes will be kept at the clinic and at CTC's Pharmacovigilance department (CTC PV) in locked and restricted areas if needed for emergency unblinding.

9.10 Blinding

This is a double-blind trial, and the allocation of treatments will not be disclosed until clean file has been declared and the database has been locked.

The IMP, *i.e.*, the C106 and the placebo oral solutions, are identical in appearance. Both solutions are colourless to yellow. Hence, it is expected that the subjects, Investigator and other site personnel will remain unaware of treatment allocation.

9.11 Emergency unblinding during the trial

The treatment code may only be broken by the Principal Investigator or delegate in case of emergency when knowledge of the treatment received is necessary for the proper medical management of the subject. The code breaking procedure should be carefully documented.

9.11.1 *Unblinding for other reasons than emergency*

The treatment code may be broken by the iSRC during the assessment process (partial unblinding) to enable their decision on continued dosing of further cohorts or to stop the dose escalation. The medical staff and the subjects will still be blinded for the treatments (active drug or placebo) to be administered in the subsequent cohorts in order to minimise bias, see Section 8.3.6.

For unblinding procedures in case of a potential suspected unexpected serious adverse reaction (SUSAR), see Section 11.3.1.14.

10 TREATMENTS

10.1 Identity of investigational medicinal products

C106 is a potent and selective nonpeptide AT_2R agonist developed by Vicore Pharma. C106 will be administered as an oral solution.

The bulk drug product will be provided to the research clinic as:

- C106 solution for oral administration; 1 mg/mL (25 mL solution in 30 mL amber vials) and 10 mg/mL (50 mL solution in 50 mL amber vials). Expressed as salt; equivalent to 0.955 mg/mL and 9.55 mg/mL of the free form.
- Placebo to C106 is a solution for oral administration, manufactured as the drug without the active pharmaceutical ingredient. Placebo will be provided in volumes of 50 mL (50 mL amber vials).

10.2 Manufacturing, packaging, labelling, and release

The IMP, including placebo, is manufactured, packaged, labelled, and released by Ardena, Ghent, Belgium.

Trained, unblinded clinical staff will prepare and label the IMP according to the randomisation schedule.

Labels will comply with applicable Good Manufacturing Practice (GMP), with Annex 13 of the European Union Good Manufacturing Practice regulations and local regulatory requirements.

The bulk IMP will be shipped to the research clinic (CTC).

10.3 Conditions for storage

The bulk drug product will be stored refrigerated at 2 to 8°C in an access-controlled storage area at CTC. The finally prepared in-use IMP can be stored at 2 to 8°C for a maximum of 24 hours.

Temperature logs will be kept for the area where the IMP is stored. The temperature should be noted on a daily basis (working days only unless automatic temperature readings are available).

The drug product must be protected from light.

10.4 Preparation and accountability

IMP preparation will be done by trained personnel, *i.e.*, a site pharmacist or a registered nurse, in a dedicated room at CTC. There will be two unblinded persons working together, one person will handle the IMP and perform the preparation according to the randomisation list and the other person will supervise the process. The personnel preparing the IMP will not be involved in any other trial activities.

CTC and the Investigator will maintain a Storage and Accountability Log as well as a Drug Dispensing Log detailing the dates and quantities of IMP received, prepared for and used by each subject and IMP returned or destroyed at the end of the trial. Any discrepancies between prepared and returned IMP must be explained and documented. Products deliberately and/or accidentally destroyed by the site or the subject must be accounted for.

10.5 Treatment administration

10.5.1 *Treatment administration Part A*

Subjects in Part A (SAD) will be administered a single oral dose of either C106 or placebo as randomised. The proposed doses are 5, 30, 60, 180, 240 and 300 mg C106.

Subjects who participate in the food interaction part will be administered a second single dose of either C106 or placebo. Any replacers in the food interaction part will receive C106 and will participate in both a fasting and a fed period.

Part A fasting conditions

Following an overnight fast of at least 10 hours, subjects will be administered the IMP with approximately 240 mL of water (including the volume of the IMP). No food is allowed for at least 4 hours post dose. During fasting, water, but no other drinks, is allowed as desired. Water is allowed *ad libitum* at the clinic except 1 hour before dose and 1 hour after dose. The IMP will be taken with water (approximately 240 mL, including the volume of the IMP).

Part A fed conditions (one cohort)

Following an overnight fast of at least 10 hours, subjects will start a high-fat, high-calorie meal 30 minutes prior to administration of the IMP (for details on the breakfast, see below). The subjects should eat this meal in 30 minutes or less, however, the IMP should be administered 30 minutes after start of the meal. No food is allowed for at least 4 hours post-dose. During fasting, water, but no other drinks, is allowed as desired. Water is allowed *ad libitum* at the clinic except 1 hour before dose and 1 hour after dose. The IMP will be taken with water (approximately 240 mL, including the volume of the IMP).

The high-fat, high-calorie breakfast will consist of the following (or equivalent): 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes (118 mL) and 8 ounces (236 mL) of whole milk. Substitutions in this meal can be made as long as the meal provides a similar number of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. The test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

10.5.2 *Treatment administration Part B*

Subjects in Part B (MAD) will be administered oral doses of C106, or placebo as randomised for 8 consecutive days. The proposed doses are 40, 100, 180 and 240 mg BID for 8 days.

Subjects will be administered the IMP with approximately 240 mL of water (including the volume of the IMP) by clinical staff from Day 1 to 8, *i.e.*, at all dosing occasions.

The first IMP dose should be taken prior to breakfast and the second dose after 12 hours, on all treatment days. On Day 8, only the morning dose will be administered. Fasting is required 2 hours before and 1 hour after both the morning and evening dose.

10.6 Continuation of treatment with Investigational Medicinal Product

This is a Phase 1 trial in healthy volunteers who will have no medical benefit from the treatment and thus there will be no treatment with C106 after end of trial participation.

10.7 Treatment compliance

In both Part A and Part B, all IMP will be administered at the research clinic under medical supervision to ensure compliance.

10.8 Return and destruction of investigational medicinal products

Any unused trial medication and all empty containers will be destructed at the site upon confirmation from the Sponsor. The Monitor will perform final IMP accountability reconciliation at the trial end to verify that all unused IMP is adequately destroyed and documented.

11 TRIAL ASSESSMENTS

The trial assessments are described in the sections below and the timing of these assessments are detailed in the schedule of events (Table 8.1-1 and Table 8.1-2 for Part A and Table 8.1-3, Table 8.1-4 and Table 8.1-5 for Part B).

11.1 Recording of data

The Principal Investigator will provide the Sponsor with all data produced during the trial from the scheduled trial assessments. The PI ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the eCRF and in all required reports.

It is important that Cardiodynamic ECG and PK blood sampling occurs as close as possible to scheduled time. In order to achieve this, the timing priority order at a particular time point is:

Part A (SAD):

1. Cardiodynamic ECG/Blood samples for PK
2. Safety laboratory samples
3. Safety 12-lead ECG
4. Vital signs

Part B (MAD):

1. Blood samples for PK
2. PD assessment (cohort B4 only)
3. Safety laboratory samples
4. Safety 12-lead ECG
5. Vital signs

Time points for PK blood sampling, PD assessment (cohort B4 only), safety laboratory samples, 12-lead ECG, and vital signs are outlined in Table 8.1-1 and Table 8.1-2 for Part A and in Table 8.1-3, Table 8.1-4 and Table 8.1-5 for Part B.

For allowed time windows for PK samples, see Section 11.4.1.

11.2 Demographics and other baseline characteristics

11.2.1 *Informed consent*

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 14.3.

11.2.2 *Eligibility criteria*

Eligibility criteria should be checked during screening and verified before randomisation. The criteria are specified in Sections 9.4 and 9.5.

11.2.3 *Demographic information*

The following demographic data will be recorded: gender, age, ethnicity, and race.

11.2.4 *Weight and height*

Weight and height will be measured without shoes. BMI will be calculated, with one decimal, from the height and weight recorded.

11.2.5 *Medical/surgical history*

Medical/surgical history will be obtained by subject interview in order to verify that the eligibility criteria are met.

The medical/surgical history should include all relevant diseases and surgeries prior to screening as judged by the Investigator.

11.2.6 *Prior and concomitant medication*

Prior medications taken within 2 weeks will be obtained by subject interview in order to verify that the eligibility criteria are met (see also Section 9.6.2).

Medications are classified as prior if the stop date was before or on the day of the first dose administration (pre-dose) and as concomitant if ongoing on the day of the first dose administration, stopped after the first dose administration or started after the first dose administration. To distinguish between prior and concomitant medications on Day 1 in each part (*i.e.,* the first dosing day), the start time of any newly introduced medication or the stop time of any previously ongoing medication must be recorded in the eCRF.

Any use of concomitant medication from screening until the last end-of-trial visit must be documented appropriately in the subject's eCRF. Relevant information (*i.e.*, name of medication, dose, dose form, unit, route, frequency, start and stop dates, reason for use) must be recorded. All changes in medication should be noted in the eCRF.

11.2.7 *HIV and Hepatitis B/C*

Subjects will be tested for HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen, hepatitis B virus surface antigen and hepatitis C virus antibodies prior to inclusion into the trial. Any positive result will exclude the subject from participating in the trial.

11.2.8 *Urine drug screen*

Urine will be screened for drugs of abuse at time points outlined in the schedule of events (Table 8.1-1 for Part A and Table 8.1-3 for Part B) using the Drug Screen Multi-12/15 Dip Test (Nal von minden) or equivalent. Additional random tests can be performed during the trial period.

11.2.9 *Alcohol test*

An alcohol test will be performed at time points outlined in the schedule of events (Table 8.1-1 for Part A and Table 8.1-3 for Part B). Additional random tests can be performed during the trial period.

11.3 Assessments related to primary endpoints

11.3.1 *Adverse events*

The Principal Investigator is responsible for ensuring that all medical staff involved in the trial is familiar with the content of this section and the content of the CTC standard operating procedures (SOPs) regarding emergencies and FIH studies.

11.3.1.1 Definition of adverse event

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

11.3.1.2 Definition of serious adverse event

An SAE is any AE which:

- results in death
- is life-threatening (this refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might had led to death if the reaction was more severe)
- requires in-subject hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (IME) (this refers to a reaction that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent any of the other outcomes defined above)

Examples of IMEs are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalisation, development of drug dependency, and drug abuse.

Planned hospitalisations or surgical interventions for a condition that existed before the subject signed the ICF and that did not change in intensity are not SAEs.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

11.3.1.3 Definition of adverse drug reaction

The term adverse reaction is to be used for all untoward and unintended responses to the IMP assessed as related to any dose administered.

11.3.1.4 Definition of serious adverse drug reaction

The term serious adverse reaction (SAR) is to be used whenever either the Investigator or Sponsor or designee assessed the SAE as related to the IMP.

11.3.1.5 Definition of suspected unexpected serious adverse reaction

A SUSAR is any SAE that has a suspected causal relationship with the IMP (assessed as related by the Sponsor or Investigator), but the nature of which is not consistent with the applicable product information (*i.e.*, the IB).

11.3.1.6 Time period and frequency for collecting adverse events

All AEs (including SAEs) will be collected from the signing of informed consent until the end-of-trial visit of each part.

Any AE with start date on the day of IMP administration must be recorded with start time.

At the end-of-trial visit, information on new AEs or SAEs, if any, and stop dates for ongoing events must be recorded as applicable.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the trial participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to the trial intervention or trial participation, the Investigator must promptly notify the Sponsor.

11.3.1.7 Assessment of intensity

The grading of the intensity of AEs will follow the CTCAE v5.0 [40]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the intensity of an AE using the following definitions, and record it on the AE Log in the eCRF:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self- care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self- care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

11.3.1.8 Assessment of causal relationship

The Investigator must assess the causal relationship between an AE and the IMP using the definitions below and record it the AE Log of the eCRF:

Related	There is a reasonable possibility that the AE was caused by the drug. There is a reasonable time relationship to drug intake. The AE cannot be explained by disease or other drugs. There may or may not be information about de-challenge or re-challenge. Disappearance of the AE upon de-challenge supports this category. Reappearance upon re-challenge is strongly supportive.
Not related	There is no reasonable possibility that the event was caused by the IMP. The temporal relationship to drug administration makes a causal relationship improbable or other drugs or underlying disease or conditions provide plausible explanations.
Not applicable	This assessment can be used *e.g.*, in cases where the subject did not receive any treatment with IMP.

11.3.1.9 Assessment of outcome

The Investigator must assess the outcome of an AE using the definitions below and record it on the AE Log of the eCRF:

Recovered/resolved	The subject has recovered completely, and no symptoms remain.
Recovering/resolving	The subject's condition is improving, but symptoms still remain.
Recovered/resolved with sequelae	The subject has recovered, but some symptoms remain (for example, the subject had a stroke and is functioning normally but has some motor impairment).
Not recovered/not resolved	The subject's condition has not improved, and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
Fatal	
Unknown	

11.3.1.10 Reporting of action taken with trial treatment

The Investigator must report the action taken with trial treatment using the definitions below and record it on the AE Log of the eCRF:

Dose increased	*Not applicable for the present trial*
Dose not changed	
Dose rate reduced	*Not applicable for the present trial*
Dose reduced	*Not applicable for the present trial*
Drug interrupted	*Not applicable for the present trial*
Drug withdrawn	
Not applicable	
Unknown	*Not applicable for the present trial*

11.3.1.11 Collecting adverse events

AEs identified using any of the following methods will be recorded:

- AEs spontaneously reported by the subject
- AEs observed by the Investigator or medical personnel
- AEs elicited based on non-leading questions from the Investigator or medical personnel

11.3.1.12 Recording adverse events

AEs must be recorded in the AE Log of the eCRF. The Investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms; start and stop dates, start and stop time; intensity; causal relationship to IMP; action taken, and outcome.

If the AE is serious, this must be indicated in the eCRF.

AEs, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

11.3.1.13 Reporting of serious adverse events

SAE reporting should be performed by the Investigator within 24 hours of awareness via the eCRF. All available information regarding the SAE should be entered in the eCRF SAE form (*i.e.*, term, intensity, causality, outcome, SAE criteria, action taken, narrative including rational for causality assessment). for the specific subject. By saving the event as "serious" in the eCRF and once the Investigator has signed-off of the event, an e-mail alert is automatically sent to predefined recipients to highlight that an SAE has been registered. The same information is automatically sent to: sae@ctc-ab.se.

The SAE report is reviewed by a designated person at CTC's Pharmacovigilance (CTC PV) department to ensure that the report is valid and correct. For fatal or life-threatening SAEs where important or relevant information is missing, immediate follow-up is undertaken and queries to the site are raised. Investigators or other site personnel should inform CTC PV of any follow-up information (including rational for changes, *e.g.*, changes in causality assessment and intensity, that should be described in the SAE narrative) on a previously reported SAE immediately but no later than within 24 hours of awareness.

If the SAE report in the eCRF is updated and signed by the Investigator, a new e-mail alert will be sent.

If any additional documentation is required (*e.g.*, autopsy report), CTC PV will request this information from the trial site.

In case the eCRF cannot be accessed, the SAE should be reported by manual completion of the paper SAE Form, provided in the Investigator Site File (ISF). The completed, signed and dated paper SAE Form should, within 24 hours, be scanned and delivered via encrypted e-mail secure file transfer to CTC's SAE inbox at sae@ctc-ab.se.

A copy of the paper SAE form must also be e-mailed to CTC at: sae@ctc-ab.se.

The trial site should notify the site Monitor via phone or e-mail about the submission of the SAE report. As soon as the site personnel have access to the eCRF, the SAE should be reported electronically as well.

The Sponsor has delegated to CTC the responsibility to report SAEs to the competent authority (CA) and IEC in accordance with local regulations.

11.3.1.14 Reporting of SUSARs to EudraVigilance, local CA and IEC

The term SAR is used whenever either the Investigator or Medical Monitor deems a blinded SAE as related to IMP. If a SAR is assessed as unexpected based on the reference safety information (RSI)/IB, it is a potential SUSAR and under such circumstances an EudraVigilance reporter will be unblinded. In case the event is regarded as a SUSAR the EudraVigilance reporter will report the SUSAR to the CA, via the EudraVigilance database, and to the IEC in accordance with local regulations and CTC SOPs within the following timelines:

- 7 calendar days if fatal or life-threatening
- 15 calendar days if non-fatal and non-life-threatening

The clock for expedited initial reporting (Day 0 = Di 0) starts as soon as the information containing the minimum reporting criteria has been received by the Sponsor. The date should be documented on an acknowledgement receipt.

The Medical Monitor is responsible for medical review of the SAE narrative in the Council for International Organisations of Medical Sciences (CIOMS) form (or equivalent) prior to expedited reporting. The CIOMS form will be reviewed and approved by the Sponsor's Medical Representative, including expectedness and causality assessment.

The Sponsor has delegated to CTC the responsibility to inform the Investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

The Sponsor or delegate is responsible for, once a year throughout the clinical trial (or on request), submitting a safety report to the CA and the IEC taking into account all new available safety information received during the reporting period.

11.3.1.15 Treatment and follow-up of adverse events

Subjects with AEs that occur during the trial must be treated according to daily clinical practice at the discretion of the Investigator.

AEs must be followed up until they have reached a "final outcome" (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved/ongoing, fatal, or unknown) or the subjects' participation in the trial ends, whichever comes first. At the end-of-trial visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded (if known). AEs assessed as stable by the Investigator at the end-of-trial visit will not have to be followed up until resolution.

It is the responsibility of the Investigator to follow up on all SAEs until the subject has reached a "final outcome" or the subjects' participation in the trial ends, whichever comes first.

SAEs and severe, non-serious AEs assessed as "Related" to IMP, still ongoing after the trial participation has ended, should be followed on a regular basis according to the Investigator's

clinical judgment until a "final outcome" has been established and to report to the Sponsor all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

11.3.1.16 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy of any female partners of male subjects, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the end of the subject's trial participation. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of the contraceptive medication.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and the Principal Investigator on the pregnancy outcomes report form.

11.3.1.17 Treatment of overdose

An overdose is a dose in excess of the dose specified for each cohort in this CTP.

Over-dosing is not likely to occur in this trial since all IMP will be administered by site personnel under medical surveillance. In cases of accidental overdose, standard supportive measures should be adopted as required.

An overdose should be documented as follows:

- An overdose with associated AE is recorded as the AE diagnosis/symptoms in the AE Log of the eCRF.
- An overdose without associated symptoms is reported in the subject's medical records.

In addition, any overdose will be recorded as a protocol deviation.

No known antidote is available.

11.3.2 ***Electrocardiogram***

Single 12-lead ECG will be recorded in supine position after 10 minutes of rest using an ECG machine. Heart rate (HR) and PR, QRS, QT and QTcF intervals will be recorded.

Safety ECGs will be reviewed and interpreted on-site by the Investigator.

Any abnormalities will be specified and documented as clinically significant or not clinically significant. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

For timing of assessments, refer to Table 8.1-1to Table 8.1-5.

11.3.3 *Telemetry*

Ambulatory ECG telemetry will be used for cardiac surveillance up to 24 hours after IMP administration in Part A (SAD).

Telemetry will be reviewed on-site by the Investigator and judged as normal, abnormal not clinically significant or abnormal, clinically significant. If judged as abnormal, clinically significant, a print-out will be saved for documentation. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

11.3.4 *Vital signs*

At visits and time points outlined in Table 8.1-1 and Table 8.1-2 (Part I) and in Table 8.1-3, Table 8.1-4 and Table 8.1-5 (Part II), systolic and diastolic blood pressure (BP) and pulse will be measured in supine position after 10 minutes of rest. Respiratory rate will be assessed. Body temperature will be measured using a digital thermometer on Day -1 of each part.

Any vital signs outside the normal ranges will be judged as not clinically significant or clinically significant. The assessment will be recorded in the eCRF. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

11.3.5 *Laboratory safety assessments*

Blood samples for analysis of clinical chemistry, haematology, and coagulation parameters will be collected through venepuncture or an indwelling venous catheter and sent to the certified clinical chemistry laboratory at Uppsala University Hospital and analysed by routine analytical methods.

Urinalysis will be performed at the research clinic using dipsticks. The assessments will be performed at visits specified in (Table 8.1-1 for Part A and Table 8.1-3 for Part B). In addition, urine sampling for analysis of the albumin/creatinine ratio will be performed at all visits where blood sampling for safety laboratory analysis is planned.

The safety laboratory parameters are defined in Table 11.3-1 and will be assessed at time-points detailed in (Table 8.1-2 for Part A and Table 8.1-4 and Table 8.1-5 for Part B).

Any lab values outside the normal ranges will be judged as not clinically significant or clinically significant. The assessment will be recorded in the eCRF. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

Table 11.3-1 Safety laboratory parameters

Category	**Parameter**
Clinical chemistry	Alanine aminotransferase (ALT)
	Albumin
	Aldosterone
	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
	Bilirubin (total and conjugated)
	Calcium
	C-reactive protein (CRP)
	Creatinine (eGFR included)

Category	Parameter
	Glucose
	Phosphate
	Potassium
	Sodium
	Urea (nitrogen)
Haematology	Haematocrit
	Haemoglobin (Hb)
	Platelet count
	Red blood cell (RBC) count
	White blood cell (WBC) count with differential count
Coagulation	Activated Partial Thromboplastin Time (APTT)
	Prothrombin Complex International Normalised Ratio (PK[INR])
Urinalysis (dipstick)	Erythrocytes
	Glucose
	Ketones
	Leucocytes
	Nitrite
	pH
	Protein
	Specific gravity
	Urobilinogen
Urinalysis (safety urine sample)	Albumin/creatinine ratio
FSH-test (at screening, postmenopausal females, questionable cases only)	Follicle stimulating hormone (FSH)

11.3.6 *Physical examination*

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, neurological, lungs, cardiovascular, and abdomen.

Any abnormalities will be specified and documented as clinically significant or not clinically significant. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

11.4 Assessments related to secondary endpoints

11.4.1 *Pharmacokinetic blood sampling and analysis*

Venous blood samples (approximately 5 mL) for the determination of plasma concentrations of C106 after administration of the IMP, will be collected through an indwelling venous catheter at the pre-specified time-points Table 8.1-2 for Part A and Table 8.1-4 and

Table 8.1-5 for Part B). Actual time for blood PK sampling must not deviate more than ±10% from the planned time except as detailed below.

Pre-dose sampling before the first dose in any Part, may be performed within 60 minutes prior to dosing.

The 24-hour and 48-hour samples in Part A should be taken within ±2 hours of the planned sampling time point.

Pre-morning dose sampling on Days 2 to 8 in Part B (MAD) must be performed immediately (within 5 minutes) before dosing.

The date and time of collection of each sample will be recorded in the eCRF.

Samples for determination of plasma concentrations of C106, will be analysed by Lablytica Life Science AB, Uppsala by means of a validated bioanalytical method. The details of the analytical method used will be described in a separate bioanalytical report.

Details on sample collection and handling will be provided in a separate laboratory manual.

11.4.2 *Urine sampling for analysis of C106*

Urine collection for the determination of C106 will be performed in Part A and in Part B (Day 1 and Day 8). In Part A, urine will be collected at visits and time intervals presented in Table 8.1-2. In Part B, urine will be collected at visits and time intervals presented in Table 8.1-4 and Table 8.1-5.

The volume of urine will be determined by total weight and documented in the eCRF. The date and time interval of each collection (start and stop time) will be recorded in the eCRF.

Three urine aliquots (5 mL) from each collection interval and pre-dose samples will be transferred to pre-labelled polypropylene cryotubes and will thereafter immediately be frozen at -70°C until analysed.

Samples for determination of urine concentrations of C106, will be analysed by Lablytica Life Science AB, Uppsala by means of a qualified bioanalytical method. The details of the analytical method used will be described in a separate bioanalytical report.

Details on sample collection and handling will be provided in a separate laboratory manual.

11.5 Assessments related to exploratory endpoints

11.5.1 *Metabolite-In-Safety Testing*

Blood sampling for future analysis of C106 metabolites will be performed at steady state in Part B (MAD), *i.e.,* from Day 8. The collection of these samples is described in Section 11.4.1. The same samples constitute an aliquot of separated plasma (750 µL) generated from each PK sample. Metabolite sampling will be performed at visits presented in Table 8.1-4 and Table 8.1-5.

Details on sample collection and handling will be provided in a separate laboratory manual.

11.5.2 *Profile of excreted metabolites in the urine*

Urine sampling (an aliquot of 5 mL urine taken from the PK urine samples) for future analysis of excreted C106 metabolites in the urine will be performed at steady state in Part B (MAD),

i.e., Day 8. The collection and handling of these samples are described in section 11.4.2 at visits presented in Table 8.1-3.

Details on sample collection and handling will be provided in a separate laboratory manual.

11.5.3 *Cardiodynamic ECG*

Twelve (12)-lead ECGs will be extracted from continuous recordings prior to and serially after dosing at time points presented in the schedule of events for Part A of the trial (Table 8.1-3). Continuous ECG recordings will be performed for 25 hours, starting 1 hour prior to dose administration and baseline ECGs will be extracted at 3 time points before dosing (-45, -30 and -15 minutes). Subjects will be supinely resting for at least 15 minutes prior to each time point for PK sampling.

The 12-lead Holter and ECG equipment will be supplied and supported by Clario. All ECG data will be collected using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12 lead digital recorder. The continuous 12-lead digital ECG data will be stored onto SD memory cards. ECGs to be used in the analyses will be selected by pre-determined time points 5 minutes before each PK sample is drawn as defined in the schedule of events (Table 8.1-3) and may be read centrally by Clario.

If a decision is made to analyse data at the Clario core laboratory, a specific analysis protocol will be developed in accordance with accepted standards for EPQT.

11.5.4 ***Pharmacodynamic assessment (Part B, cohort B4)***

The PD effect on endothelial function will be assessed by EndoPAT at visits and time points specified in the schedule of events for Part B of the trial (Table 8.1-3 and Table 8.1-4) according to the manufacturer's instructions. The EndoPAT assessments should be done at approximately the same time of the day on both occasions.

The EndoPAT assessment will be conducted in a quiet and relaxed atmosphere. Before initiating the assessment, the subject will be supine for at least 15 minutes. The subjects will be instructed to remain as still as possible during the assessment period. EndoPAT bio sensors will be placed on the subjects right and left index fingers. If this finger is unsuitable (e.g., finger is cut or injured), a different finger may be used as long as the same finger is used on both hands. The same finger should preferably be used at both assessments. A cuff will be placed on the nondominant upper arm for occlusion of the brachial artery.

Each recording will consist of a 5-minute baseline assessment, a 5-minute occlusion assessment, and 5-minute post-occlusion assessment. During the post-occlusion period, blood flow is restored causing an endothelium-dependent vasodilation.

The EndoPAT software, provided with the device, will calculate the RHI and AI scores using a computerised automated algorithm as outlined below. The results will be recorded in the eCRF.

- RHI score: post-to-pre occlusion pulse amplitude tonometry signal ratio in the occluded arm relative to the same ratio in the control arm, and corrected for baseline vascular tone. RHI is a measure of endothelial function.

- AI: calculated from pulse amplitude tonometry pulses at the baseline period. AI is a measurement of vascular stiffness and reflects the structural nature and basal tonus of the vessel.

The time points of the initiation and completion of the EndoPAT assessment, the arm occluded, the fingers assessed and any significant deviations from the instructions for use will be recorded in the eCRF.

11.6 Appropriateness of measurements

The stopping rules for dose escalation used (see Section 8.3.4) follows the recommendations and grading system of CTCAE v5.0 [40] but also take into account the recommendations published by Sibille et al 2010 [41], which is an adaptation to FIH studies of the grading systems previously proposed by NCI [1], WHO [42], NIH [43] and FDA [44].

EndoPAT is an FDA-cleared, non-invasive device commonly used to assess endothelial function.

All other methods used for safety assessments are commonly used in standard medical care and in Phase 1 clinical trials. Non-compartmental analysis (NCA) of PK parameters is standard for Phase 1 clinical trials.

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

The sample collection procedure for PK analysis is described in Section 11.4.1.

Safety laboratory samples are collected according to standard procedures.

12.2 Volume of blood

The anticipated volume of blood samples collected during the trial from each subject will not exceed 450 mL (*i.e.*, less than the volume drawn during a regular blood donation).

Estimated blood volumes to be collected are presented in Table 12.2-1.

Table 12.2-1 Estimated blood volumes

Category	**Estimated number of sampling occasions**	**Estimated volume per occasion**	**Estimated total volume**
Part A			
Clinical chemistry, haematology, coagulation[1]	5	14 mL	70 mL
Aldosterone	5	4 mL	20 mL
HIV, Hepatitis B/C	1	4 mL	4 mL
PK sampling	14	5 mL	70 mL
Total:			**164 mL**
Part B			
Clinical chemistry, haematology, coagulation	7	14 mL	98 mL
Aldosterone	7	4 mL	28 mL
HIV, Hepatitis B/C	1	4 mL	4 mL
PK sampling	32	5 mL	160 mL
Total:			**290 mL**

1. FSH test in females only (questionable cases), estimated volume: 4 mL.

12.3 Handling, storage and destruction of laboratory samples

All biological samples will be stored in a biobank at CTC (Biobank #893).

Any remains from the safety laboratory samples will be disposed of after analyses.

The samples for analyses of PK (blood and urine) and metabolites will be stored at <-70°C until analysed. The PK samples will be disposed of after the CTR has been finalised. The samples for MIST analysis will be sent to Admescope, Södertälje, Sweden. The MIST samples will be disposed once analysed but may be stored for a maximum of 10 years prior to analysis.

12.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

CTC keeps full traceability of collected biological samples from the subjects while in storage at the research clinic until shipment and keeps documentation of receipt of arrival.

The sample receiver (the analytical laboratory) keeps full traceability of the samples while in their storage and during use until used or disposed of.

The Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of trial sites, and auditing of external laboratory providers.

12.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of biological samples donated, the samples will be disposed of/destroyed, if not already analysed and documented.

The Principal Investigator will ensure that:

- Subject withdrawal of informed consent is notified immediately to Sponsor.
- Biological samples from the subject if stored at the research clinic, are immediately identified, disposed of/destroyed and the action is documented.

The Sponsor has to ensure that the laboratory holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed or returned to the research clinic and the action is documented.

13 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Quality management: critical process, system and data identification

During CTP development, the Sponsor will identify those processes, systems (facilities, computerised systems), and data that are critical to ensure human subject protection and the reliability of trial results according to applicable SOPs and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 R2.

Identified risks, including risks associated with the COVID-19 (coronavirus disease 2019) pandemic, will be categorised separately from the CTP.

In relation to the COVID-19 pandemic, trial conduct/procedures including *e.g.*, monitoring, AE reporting, safety monitoring, changes in investigators and key trial team staff and quality assurance (QA) activities may need to be reassessed and temporary, alternative proportionate mechanisms of trial conduct/procedures may be required. All changes to the original plan will be documented.

13.2 Quality assurance and quality control

The Sponsor is responsible for implementing and maintaining QA and quality control (QC) systems with written SOPs with regards to management of identified risks, CTP compliance, good clinical practice (GCP) compliance and applicable regulatory requirements.

The Sponsor is responsible for securing agreements with involved subcontractors and to perform regular subcontractor oversight to ensure CTP compliance, GCP compliance, and compliance with applicable regulatory requirements.

The Sponsor is responsible for implementing a risk-based validated electronic data capture system and maintain SOPs for the whole life cycle of the system.

QC should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The Sponsor has delegated the responsibilities outlined above to CTC whilst maintaining overall trial oversight.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the trial

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [47] and are consistent with the ICH E6 (R2) guideline for GCP [48], the EU Clinical Trials Directive 2001/20/EC [49], and applicable local regulatory requirements.

14.2 Ethics and regulatory review

The Principal Investigator is responsible for submission of the CTP, the subject information and ICF, any other written information to be provided to the subjects, and any advertisements used for recruitment of subjects to applicable IEC for approval.

The Sponsor is responsible for submission of trial documents to the applicable Competent Authorities (CAs) according to local regulatory requirements.

Approval must be obtained in writing from both IEC and CA before the first subject can be recruited.

The Sponsor will provide the CA, IEC, and Principal Investigators with safety updates/reports according to local requirements. Progress reports and notifications of SUSARs will be provided to the IEC according to local regulations and guidelines.

14.3 Subject information and consent

It is the responsibility of the Investigator or an authorised associate to give each potential trial subject adequate verbal and written information before any trial specific assessments are performed.

The information will include the objectives and the procedures of the trial as well as any risks or inconvenience involved. It will be emphasized that participation in the trial is voluntary and that the subject may withdraw from participation at any time and for any reason, without any prejudice. All subjects will be given the opportunity to ask questions about the trial and will be given sufficient time to consider participation before signing the ICF.

Before performing any trial-related procedures the ICF must be signed and personally dated by the subject by the Investigator. A copy of the subject information including the signed ICF will be provided to the subject.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the eCRF. The subject information sheet and the signed ICF should be filed by the Investigator for possible future audits and/or inspections.

The final approved version of the subject information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

14.4 Subject participation card

The subject will be provided with a Subject participation card including the following information:

- That he/she is participating in a clinical trial
- Subject trial ID
- That he/she is treated with the IMP
- The name and phone number of the Investigator
- Name and address of the Sponsor

14.5 Subject data protection

The ICF includes information that data will be recorded, collected and processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union general data protection regulation (GDPR), Regulation (EU) 2016/679 [50] the data will not identify any persons taking part in the trial.

The potential trial subject should be informed that by signing the ICF he/she approves that authorized representatives from Sponsor and CTC, the concerned IEC and CA have direct access to his/her medical records for verification of clinical trial procedures. For further details on the subject information and ICF process, refer to Section 14.3.

The subject has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete in accordance with the GDPR (EU) 2016/679 and the request will be raised to the Principal Investigator.

The Investigator must file a Subject Identification List which includes sufficient information to link records, i.e., the eCRF and clinical records. This list should be preserved for possible future inspections/audits but must not be made available to the Sponsor except for monitoring or auditing purposes.

Personal data that are collected in the trial such as health information and ethnicity are considered as sensitive personal data. This data will be pseudonymised, i.e., personally identifiable information (PII) will be removed and replaced by a unique subject ID and will be processed by the Sponsor and other involved parties during the trial.

For this trial, the Sponsor is the data controller of all data processed during the trial (e.g., Trial Master File [TMF], trial reports) and CTC AB is the data processor. Any subcontractors used in the trial, are also data processors.

For data that are processed at the clinic(s) (e.g., medical records and ISF), CTC AB is the data controller.

14.6 Changes to the approved clinical trial protocol

Any proposed change to the approved final CTP (including appendices) will be documented in a written and numbered clinical protocol amendment. All substantial amendments to the protocol must be approved by the appropriate IEC and/or CA before implementation according to applicable regulations.

14.7 Audits and inspections

Authorised representatives of Sponsor, a CA, or an IEC may perform audits or inspections at the research clinic, including source data verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all trial-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, ICH-GCP guidelines and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a CA about an inspection at the centre. The Investigator will provide direct access to source data and documents in case of audits and inspections.

14.8 Insurance

Subjects will be covered under a liability insurance policy through the Swedish Pharmaceutical Insurance (Läkemedelsförsäkringen). The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating subjects are also protected in accordance with national regulations, as applicable. CTC has a company insurance covering services performed by CTC.

15 TRIAL MANAGEMENT

15.1 Training of trial site personnel

Before enrolment of the first trial subject a Sponsor representative or delegate will perform a site initiation visit at the research clinic. The requirements of the CTP and related documents will be reviewed and discussed, and the investigational staff will be trained in any trial specific procedures and system(s) utilised.

It is the responsibility of the Investigator to ensure that all personnel involved in the trial are fully informed of all relevant aspects of the trial and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this trial must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the trial together with their function and trial related duties delegated. A Curriculum Vitae will be available for all staff to whom trial-specific duties are delegated.

15.2 Clinical monitoring

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities. The Investigator will permit trial related monitoring providing direct access to source data and documents.

As defined in the risk-based monitoring (RBM) plan, approved by the Sponsor and provided separately, the responsible Monitor will periodically visit the trial site at times agreed upon by the Investigator and the Monitor. Adaptations related to the on-site monitoring plan, when it is impossible or inappropriate to follow due to the COVID-19 pandemic, may be required such as supplementation with (additional/increased) centralised monitoring and central review of data if considered possible and meaningful. Results of adjusted monitoring/review measures should be reported to the Sponsor in monitoring reports and in the CTR. At the time of each monitoring visit, the role of the Monitor is (but not limited to) to:

- provide information and support to the investigational team.
- confirm that facilities and resources remain acceptable.
- confirm that the investigational team is adhering to the CTP, applicable SOPs, guidelines, manuals and regulatory requirements.
- verify that the correct informed consent procedure has been adhered to for participating subjects
- verify that data are being accurately and timely recorded in the eCRFs and that IMP accountability checks are being performed.
- verify that data in the eCRF are consistent with the clinical records (SDV) in accordance with the RBM plan.
- ensure that withdrawal of informed consent to the use of the subject's biological samples will be reported and biological samples are identified and disposed of/destructed accordingly, and that this action is documented and reported to the subject.

- verify that AEs are recorded and reported in a timely manner and according to the CTP.
- raise and escalate any serious quality issues, serious GCP breach, and any data privacy breach to the Sponsor.

Centralised monitoring will also be performed continuously by trial team members at CTC in accordance with the RBM plan.

When the trial has been completed and all queries have been resolved and the database has been locked, the Monitor will perform a close-out visit.

15.3 Source data documents

A separate Origin of Source Data List will be generated for each site before start of enrolment, specifying the location of the source of derived information appearing in the eCRF. This document must be signed by the Principal Investigator and the Monitor to confirm agreement before start of recruitment.

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the trial. They include laboratory notes, memoranda, material dispensing records, subject files, etc. The eCRF may constitute source data if clearly defined in the Origin of Source Data List.

The Investigator should guarantee access to source documents to the Monitor, CAs, and the IECs, if required.

15.4 Trial agreements

The Principal Investigator must comply with all the terms, conditions, and obligations of the Clinical Trial Agreement for this trial.

Agreements between Sponsor and CTC must be in place before any trial-related procedures can take place, or subjects be enrolled.

15.5 Trial timetable and end of trial

The trial is expected to start in Q2 2022 and to be completed by Q3 2023.

A subject is considered to have completed the trial if he/she has completed all visits in the trial including the end-of-trial-visit.

The end of the trial is defined as the date of the last visit of the last subject in the trial.

15.6 Termination of the trial

The Investigator or the Sponsor may terminate this trial prematurely for any reasonable cause. The IEC and CA should be informed promptly. Conditions that may warrant trial termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the trial or potential trial subjects; or
- A decision by the Sponsor to suspend or discontinue development of the IMP.
- If the CA obtains information that raises doubts about the safety or scientific validity of the clinical trial, the CA can suspend or prohibit the trial. Before the CA reaches its decision, it shall, except where there is imminent risk, ask the Sponsor and/or the

Investigator for their opinion, to be delivered within 1 week (Directive 2001/20/EC, Article 12, Section 1).

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

15.7 Reporting and publication

15.7.1 *Clinical trial report*

A summarising report must be submitted to the applicable CA and IEC within 12 months after completion of the trial (in accordance with LVFS 2011:19, Chapter 9).

A CTR in compliance with ICH-E3, describing the conduct of the trial, any statistical analyses performed and the results obtained, will be prepared by CTC. The report will be reviewed and approved by, as a minimum, the Principal Investigator, the Statistician and the Sponsor. The trial results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the trial.

All data obtained from any exploratory analyses will be reported separately.

15.7.2 *Annual safety report*

If the trial duration exceeds one year, the Sponsor must submit development safety update report (DSUR) to the CA and to the IEC. The report shall summarise all pertinent safety information collected during the reporting period and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical trial.

15.7.3 *Confidentiality and ownership of trial data*

Any confidential information relating to the IMP or the trial, including any data and results from the trial, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the trial are responsible for protecting the confidentiality of this proprietary information belonging to the Sponsor.

15.7.4 *Publication*

The results from this trial may be submitted for publication at the discretion of the Sponsor.

15.8 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6 GCP, Section 8) for 25 years after finalisation of the CTR. This includes any original source documents related to the trial, the Subject Identification List (providing the sole link between named subject source records and anonymous eCRF data), the original signed ICFs and detailed records of disposition of IMP.

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

The Sponsor will archive the TMF in accordance with ICH E6 GCP, Section 8 and applicable regulatory requirements.

The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the clinic and filed in the Investigator Trial File for archiving for 25 years after finalisation of the CTR.

The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorised representatives of appropriate Health/Regulatory Authorities, without written permission from the Sponsor.

16 DATA MANAGEMENT

The data management routines include procedures for handling of the eCRF, database set-up and management, data entry and verification, data validation, QC of the database, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the CTP.

Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of computerised online edit checks identifying *e.g.*, data values that are outside the allowed range and SAS-programmed batch checks on data exports. All trial-specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

Detailed information on data management will be described in a trial-specific Data Management Plan (DMP).

16.1 The web-based eCRF

Clinical data will be entered into a 21 CFR Part 11-compliant eCRF (Viedoc™) provided by Viedoc Technologies AB. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents or at bedside (if the eCRF data constitutes source data). Source data are to be defined at the site before inclusion of the first subject (Section 15.3).

Authorised site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorised trial site personnel prior to the trial being initiated and any data being entered into the system for any trial subject.

16.2 The entering of data into the eCRF

All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other trial team member besides site staff can enter data in the eCRF. All data should be entered in English. The eCRFs should be completed as soon as possible (within 24 hours in case of an SAE) during or after the subject's visit. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or assigned clinical staff should record such information in the eCRF. The Investigator will be required to electronically sign off the clinical data. This will be performed by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature.

16.3 The query process

The Monitor will review the eCRFs and evaluate them for completeness and consistency. Data in the eCRF will be compared with the respective source documents to ensure that there are no discrepancies for critical data as described in the RBM plan. All entries, corrections, and alterations are to be made by the Investigator or designee.

If corrections are needed, queries will be raised within the eCRF, either as a result of built-in edit checks or manually raised by the monitor. An appropriate member of the site staff will

answer the queries in the eCRF either by correcting the data or by entering a response to the query. The monitor will either approve the answer/correction or re-issue the query.

16.4 Audit trail

All entries in the eCRF will be fully recorded in a protected audit trail. Once clinical data have been saved, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged.

16.5 External data

External data consists of data that are not recorded in the eCRF. Data will be received in electronic format. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed with the external data provider.

External data in the present trial are safety laboratory data, cardiodynamic ECG data and plasma and urine concentration data, and EndoPAT data.

16.6 Medical coding

Medical coding will be performed by trained personnel at CTC. AEs and medical/surgical history verbatim terms will be coded using the Medical Dictionary of Regulatory Activities (MedDRA; latest version available at start of coding). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Anatomic Therapeutic Chemical (ATC) classification system. All coding will be approved by Sponsor prior to database lock.

16.7 Database lock

When all data have been entered, all external data have been received and discrepancies solved, clean file will be declared, the database will be locked, the randomisation code will be broken and the data will be analysed.

17 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate Statistical Analysis Plan (SAP), which will be signed and approved prior to database lock.

Analyses of the primary and secondary endpoints will be performed by CTC.

17.1 General

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, SD, median, minimum and maximum value.

Categorical data will be presented as counts and percentages and by means of absolute and relative frequencies where applicable.

All descriptive statistics will be presented by part, assigned treatment (dose cohort or placebo) and by assessment time where applicable.

Individual subject data will be listed by part, treatment, subject number, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC).

The baseline measurement will be defined as the latest measurement prior to the first administration of the IMP.

No imputation of missing data will be performed.

17.2 Determination of sample size

No formal sample size calculation has been performed for this trial. The proposed sample size is considered sufficient to provide adequate information for the trial objectives.

Approximately 144 subjects will be screened to achieve a total of 72 randomised and dosed subjects. The number may increase if additional dose cohorts need to be investigated and/or if recommended by the iSRC.

17.3 Analysis data sets

17.3.1 *Full analysis set*

The Full Analysis Set (FAS) will consist of all subjects who have been randomised and received at least one dose of IMP and who has at least one post-baseline assessment of data. The FAS will be used for all safety and PD evaluations.

17.3.2 *Pharmacokinetic analysis set*

The Pharmacokinetic analysis set (PKAS) will consist of all subjects who received at least one dose of the trial drug and provided an plasma concentration data and who have no AEs or

protocol deviations judged to affect the PK analysis. Individual PK values may be excluded from the analysis as specified in the SAP.

17.4 Description of trial population

17.4.1 *Demographics and baseline characteristics*

Descriptive statistics for demographics, weight, height and BMI, will be presented by treatment and cohort. All data will be listed by part, treatment and subject.

17.4.2 *Medical/surgical history and prior/concomitant medication*

Medical/surgical history will be presented by SOC and preferred term (PT). Prior/concomitant medications will be presented by ATC level 3 and 5. All data will be listed by part, treatment and subject.

17.4.3 *Treatment compliance*

Individual dose(s) will be listed by part, treatment and subject.

17.5 Analysis of primary endpoints

17.5.1 *Adverse events*

An overview of all AEs, including SAEs, intensity, and relationship to IMP will be presented. Incidence of AEs and SAEs will be summarised by SOC and PT by part, cohort, treatment and overall. An overview of any related AEs will be summarised by SOC and PT if considered appropriate.

All AE data will be listed by part, treatment, and subject and include the verbatim term entered by the Investigator.

17.5.2 *12-lead ECG*

All ECGs will be categorised as" normal", "abnormal", "not clinically significant", or "abnormal, clinically significant" (as judged by the Investigator) and summarised by treatment and cohort using frequency tables. Changes over time will be presented using shift tables, if considered appropriate. All data will be listed by part, cohort, treatment, and subject.

17.5.3 *Vital signs*

Vital signs (systolic/diastolic BP, pulse and respiratory rate) will be summarised by part, treatment, and cohort. Data will be presented with absolute change from baseline. All data will be listed by part, cohort, treatment, and subject.

17.5.4 *Safety laboratory analyses*

Safety laboratory data will be summarised by treatment and cohort with absolute change from baseline at each visit. Abnormal, clinically significant values will be summarised separately, if considered appropriate. All data will be listed by part, cohort, treatment, and subject.

17.5.5 *Physical examination*

Clinically significant and non-clinically significant abnormal findings will be specified and presented by subject and summarised by treatment and cohort. Changes over time will be presented using shift tables, if considered appropriate. All data will be listed by part, cohort, treatment, and subject.

17.6 Analysis of secondary endpoints

17.6.1 *Analysis of pharmacokinetics*

The PK analysis will be based on the PK analysis set and performed by CTC. The PK parameters will be calculated by non-compartmental analysis (NCA) using the software Phoenix WinNonlin® version 8.1 or later (Certara, U.S.A.).

Part A, SAD:

- The following non-compartmental PK parameters will be assessed:
  - AUC_{inf}
  - $AUC_{0\text{-}last}$
  - C_{max}
  - T_{max}
  - $T_{½(z)}$
  - CL/F
  - V_z/F
  - Relative bioavailability for fasted versus fed cohort.

In addition, dose proportionality after a single dose, based on AUC_{inf} and C_{max} will be analysed. Assessment of dose proportionality will be performed by a power model.

All PK parameters will be calculated both for the fasted and the fed cohort.

Part B, MAD:

The following non-compartmental PK parameters will be assessed:

- PK parameters after first dose:
  - AUC_{tau}
  - AUC_{inf}
  - C_{max}
  - T_{max}
  - $T_{½(z)}$
  - CL/F
  - V_z/F
- PK parameters after last dose:
  - AUC_{tau}
  - C_{max}
  - T_{max}
  - $T_{½(z)}$
  - CL/F
  - V_z/F

In addition, dose proportionality based on AUC_{tau} and C_{max} and accumulation ratios based on AUC_{tau} and C_{max} will be analysed. Assessment of dose proportionality will be performed by a power model using 90% power.

Observed concentration at the end of a dosing interval, immediately before next administration (C_{trough} from Days 2 to 8, pre-morning dose samples) will also be calculated to assess steady state.

Urine excretion (evaluated in Part A and in Part B part at steady state):

- % of dose and absolute amount excreted unchanged in the urine
- Renal clearance.

Summary statistics for the PK parameters will be presented by treatment and cohort with number of measurements, arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, minimum, maximum, geometric mean and geometric CV (CV%).

All data will be listed by part, cohort, treatment, and subject.

Additional PK parameters may be calculated if considered appropriate.

17.7 Analysis of exploratory endpoints

The exploratory endpoints (MIST, urine metabolites and endothelial function) may be reported separately from the CTR. Cardiodynamic ECG data will be stored for potential future evaluation and will thus not be included in the CTR.

Details of the analyses will be given in the SAP, if applicable.

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19 SIGNATURES

19.1 Principal Investigator statement

I have read and understood this CTP and agree to conduct the trial accordingly and to comply with the Investigator obligations stated in this CTP, GCP and applicable regulatory requirements.

Principal Investigator

19.2 Signature page (approval of the clinical trial protocol)

Sponsor signatories