Clinical Trial Protocol and Statistical Analysis Plan

Title:	**A phase 1, open-label, single-centre study investigating the effect of C21 on forearm blood flow in healthy male subjects by use of strain-gauge venous occlusion plethysmography**
Trial ID:	**VP-C21-009**
NCT No.:	**NCT05277922**
Version:	**2.0**
Date:	**09-Mar-2022**

Clinical Study Protocol	
EudraCT No.	2021-000288-62
Test Product	Compound 21 (C21)
Sponsor study code	VP-C21-009
Protocol Version and Date	Final v2.0; 09MAR2022

A phase 1, open-label, single-centre study investigating the effect of C21 on forearm blood flow in healthy male subjects by use of strain-gauge venous occlusion plethysmography

Test product	C21
Comparator product	Nipruss® (sodium nitroprusside)
Sponsor signatories	[redacted] Vicore Pharma AB Kronhusgatan 11 SE-411 05 Gothenburg, Sweden
Principal Investigator	[redacted] CTC Clinical Trial Consultants AB
Clinical study conduct and management	CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden and CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance 85, 2nd level SE-751 85 Uppsala, Sweden

1 STUDY SYNOPSIS

Study title A phase 1, open-label, single-centre study investigating the effect of C21 on forearm blood flow in healthy male subjects by use of strain-gauge venous occlusion plethysmography	
Study code VP-C21-009	**EudraCT No** 2021-000288-62
Planned study period Q1 2022	**Phase of development** Phase 1
Principal Investigator [redacted] CTC Clinical Trial Consultants AB, Uppsala University Hospital, Uppsala, Sweden	
Study design This is a phase 1, open-label, single-centre study investigating the effects of intra-arterial (i.a.) infusions of the angiotensin II type 2 receptor (AT_2R) agonist Compound 21 (C21) on forearm blood flow (FBF) in healthy male subjects by use of strain-gauge venous occlusion plethysmography.	
Objectives Primary objective To investigate the effect of C21 on FBF measured by strain-gauge venous occlusion plethysmography in healthy male subjects. Secondary objectives – To establish the dose-response curve for C21. – To explore the method of measuring FBF by strain-gauge venous occlusion plethysmography by using sodium nitroprusside as a positive control. – To evaluate safety and tolerability of i.a. administrations of C21 to healthy male subjects.	
Endpoints Primary endpoint Percent change from baseline in FBF, in response to increasing i.a. doses of C21. Secondary endpoints – Dose-response curve of C21. – Percent change from baseline in FBF, in response to increasing i.a. doses of sodium nitroprusside. – Frequency, intensity, and seriousness of adverse events (AEs). – Clinically significant changes in vital signs, ECG and safety laboratory parameters.	
Number of subjects planned Approximately 10 subjects will be screened to achieve 5 completed subjects with evaluable FBF data.	
Diagnosis and main eligibility criteria Healthy male subjects between 18-45 years of age and a body mass index (BMI) of 18.5-30.0 kg/m^2, good general health and fulfilling all the inclusion criteria and none of the exclusion criteria.	

Methodology

Consenting subjects will be screened for eligibility according to study-specific eligibility criteria within 30 days prior to investigational medicinal product (IMP) administration (Visit 1; screening).

Eligible subjects will be scheduled for a treatment visit (Visit 2; Day 1) . Relevant inclusion/exclusion criteria will be confirmed and a standardised meal (breakfast or lunch depending on the time of the day) will be served 60 minutes (min) prior to the first FBF measurement.

Measurements of FBF will be performed using a Conformité Européenne (CE)-marked automated strain-gauge venous occlusion plethysmography equipment providing on-line measurements, following a pre-specified procedure.

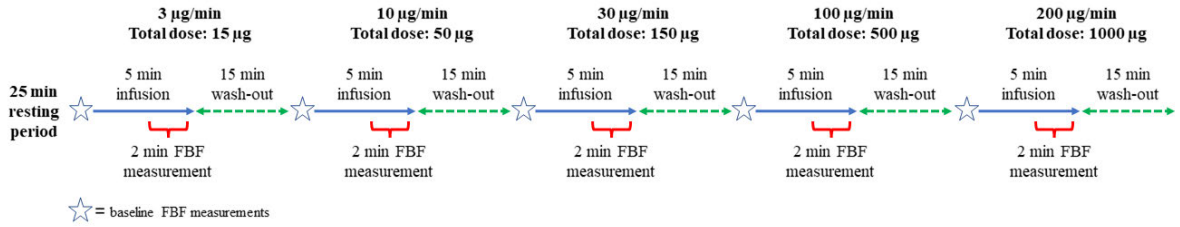
The subject will be placed resting in a comfortable supine position in a quiet room with normal room temperature (+20 to +25º C) with the forearms positioned above the level of the heart. Cuffs will be placed on the widest part of both forearms and a smaller cuff will be placed around each wrist. The non-infused arm is used as a contemporaneous control to account for any minor changes in FBF affecting both arms, *e.g.* emotional stress or temperature changes.

A catheter will be inserted into the brachial artery of the nondominant arm following standard hospital procedures and a resting period of approximately 25 min will follow. At the end of this resting period, baseline measurements of FBF will be performed.

Ascending doses of C21 (3, 10, 30, 100 and 200 µg/min) will be administered through local i.a. infusions for 5 min/dose with an infusion rate of 1 mL/min or 2 mL/min for the 200 µg/min dose. Measurements of FBF will be performed in both arms simultaneously during the last 2 min of each infusion/dose. The C21 doses will be separated by a wash-out period of at least 15 min. At the end of each wash-out period, FBF will be measured and a baseline value for the next dose will be recorded. The Investigator will assess any emerging AEs by subject interview between each dose before deciding to proceed to the next dose level.

A flow-chart of the C21 dosing and FBF measurement schedule is presented in Figure 1.

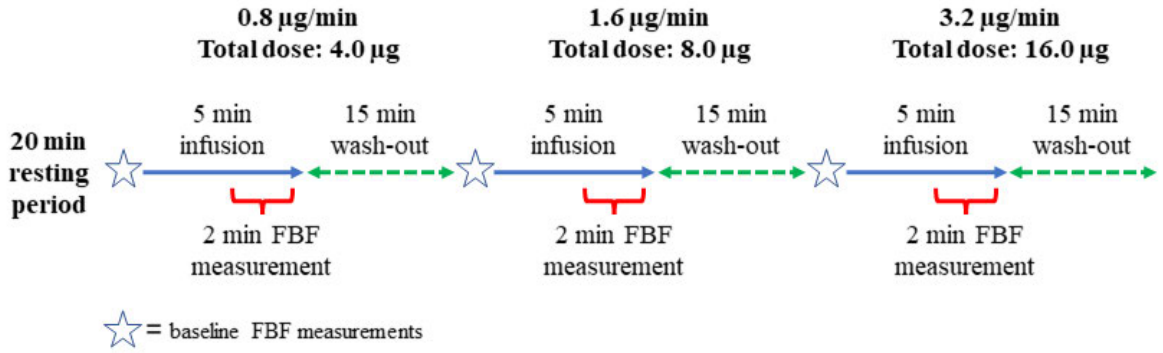
Figure 1 Dosing and measurement flow-chart for C21 infusions



When the last C21 dose has been administered there will be a resting period of 20 min. At the end of this resting period, FBF will be measured and a baseline value for the first sodium nitroprusside dose will be recorded.

Infusions of sodium nitroprusside solution (Nipruss®) will be performed as a positive control, using the same methodology as described above. Ascending doses of 0.8, 1.6, and 3.2 µg/min will be administered. A flow-chart of the Nipruss® dosing and FBF measurement schedule is presented in Figure 2.

Figure 2 Dosing and measurement flow-chart for Nipruss® infusions



Safety assessments (blood pressure, pulse, electrocardiogram [ECG], and safety laboratory parameters) will be performed prior to first dose of IMP and before the subject leaves the clinic. Any occurrence of AEs during the procedure will be recorded.

After removal of the arterial catheter a compression bandage will be applied to prevent bleeding. Written instructions regarding how to handle the bandage, how to manage symptoms and when and how to contact the Investigator if necessary, will be provided to the subject before leaving the clinic.

A follow-up phone call (end-of-study) will be performed 7 to 10 days after the treatment visit (Visit 2).

Investigational med Investigational medicinal product, dosage and mode of administration

Test product

C21 is a novel first in class selective AT_2R agonist. Activation of AT_2R causes dilatation of blood vessels and inhibition of inflammation, apoptosis, and fibrosis, and is thus considered to play a beneficial counter-regulatory role to the effects of angiotensin II type 1 receptor (AT_1R) activation.

C21 solution for local i.a. infusion will be provided in concentrations of 30 µg/mL and 100 µg/mL. These concentrations will be diluted with 0.9% saline to achieve the two lower doses. The solution will be infused through a catheter placed in the brachial artery. Ascending doses of 3, 10, 30, and 100 µg/min will be administered to each subject with an infusion rate of 1 mL/min. For the dose of 200 µg/min, the infusion rate will be 2 mL/min. Each infusion will last for 5 min.

Comparator product (positive control)

Nipruss® powder for solution (active ingredient sodium nitroprusside dihydrate) will be used as a positive control due to the potent vasodilative properties of sodium nitroprusside. Each ampoule of Nipruss® contains 60 mg sodium nitroprusside dihydrate powder corresponding to 53 g water free sodium nitroprusside. The powder will be dissolved in water for injection solution or in a 5% glucose solution. This concentrated solution will be diluted with a 5% glucose solution to achieve the doses to be administered i.a. (0.8, 1.6, and 3.2 µg/min).

Duration of treatment

Each subject will receive up to 5 infusions with C21 and 3 infusions with the positive control. The duration of each infusion will be 5 min. The duration of treatment, including resting and wash-out periods, will be approximately 4 hours.

Duration of each subject's involvement in the study

Each subject will be involved in the study for a maximum of 41 days, including screening and end-of-study follow-up call.

Efficacy assessments

Strain-gauge venous occlusion plethysmography will be used for measurements of FBF.

Safety assessments

- Vital signs (blood pressure and pulse)
- 12-lead ECG
- Safety laboratory parameters
- Adverse events reporting

Statistical methods

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

The full analysis set (FAS) will consist of all subjects who have been included and received at least one dose of IMP and have at least one post-baseline assessment.

The safety analysis set will compromise all subject who received at least one dose of the IMP.

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

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment (test product/comparator), and by assessment time. Individual subject data will be listed by subject number, treatment, 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).

Baseline for safety assessments will be defined as the last data collection point prior to the first administration of IMP. For the FBF measurements, a baseline will be defined for each dose level.

No imputation of missing data will be performed.

The response to increasing i.a. doses of C21 will be summarised using descriptive statistics with percent change from baseline and presented by dose.

The dose response curve of C21 will be presented using a mixed model. The natural logarithm of the maximum FBF value for each dose level and each subject will be used as the dependent variable in the model. Kenward-Roger's approximation for degrees of freedom will be used. The least square means (LSMeans) estimates for the doses will be presented in a plot. In addition, the pairwise LSMeans differences between the doses will be tabulated.

Study reporting

After completion of the study, an International Council for Harmonisation (ICH) E3 compliant Clinical Study Report (CSR) will be prepared.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
AE	Adverse event
Ang II	Angiotensin II
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
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 curve
BCRP	Breast cancer resistance protein
Bpm	Beats per minute (unit for pulse measurement)
BMI	Body mass index
BUN	Blood urea nitrogen
C21	Compound 21
CA	Competent authority
CE	European Conformity (“Conformité Européenne”)
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CRO	Contract research organisation
CSP	Clinical study protocol
CSR	Clinical study report
CTC	Clinical Trial Consultants AB
CYP	Cytochrome P450 enzymes
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
eNOS	Endothelial nitric oxide synthase
EVF	Erythrocyte volume fraction

Abbreviation or term	Explanation
FAS	Full analysis set
FBF	Forearm blood flow
GCP	Good clinical practice
GDPR	General data protection regulation
GMP	Good manufacturing practice
Hb	Haemoglobin
HIV	Human immunodeficiency virus
i.a.	Intra-arterial
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of technical requirements for pharmaceuticals for human use
IEC	Independent ethics committee
IME	Important medical event
IMP	Investigational medicinal product
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LSMeans	Least square means
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MDR1	Multi-drug resistance 1
MedDRA	Medical dictionary for regulatory activities
NO	Nitric oxide
NOAEL	No-observed-adverse-effect-level
NSAID	Non-steroidal anti-inflammatory drug
OAT3	Organic anion transporter
OATP1B1	Organic anion transporting polypeptide 1B1
PII	Personally Identifiable Information
PK(INR)	Prothrombin complex international normalised ratio
PT	Preferred term
QA	Quality assurance
QC	Quality control

Abbreviation or term	Explanation
RAS	Renin-angiotensin system
RBC	Red blood cell
RBM	Risk-based monitoring
RSI	Reference safety information
SAR	Serious adverse reaction
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SDV	Source data verification
SLC	Solute carrier
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class
SOP	Standard operating procedures
SuHx	Sugen-hypoxia
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent AE
TMF	Trial master file
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 study. **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 contact the Medical Monitor (Table 4.1-1).

Table 4.1-1 **Medical emergencies contact**

Name	Function in the study	Telephone number and e-mail
[redacted]	Medical Monitor	[redacted]

5 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor

Vicore Pharma AB
Kronhusgatan 11
SE-411 05 Gothenburg, Sweden

Sponsor Signatories

[redacted]

Sponsor's Project Manager

[redacted]

Sponsor Study Physician

[redacted]

Clinical conduct

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

Principal Investigator

[redacted]

Study management

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

Clinical Research Manager

[redacted]

Biostatistician

[redacted]

Medical Monitor

[redacted]

Medical Writer

[redacted]

Evaluation of plethysmography data	[redacted]
Laboratory (HIV and hepatitis)	Clinical Microbiology Dag Hammarskjölds väg 38 SE-752 37 Uppsala, Sweden
Laboratory (safety parameters)	Clinical Chemistry and Pharmacology Uppsala University Hospital Entrance 61, 2nd level SE-751 85 Uppsala, Sweden
Manufacturing, packaging, labelling of test product (C21)	Ardena Kleimor 4 B-9030 Mariakerke, Belgium
Release of test product (C21) and shipment to site	ClinStorage AB Banvaktsvägen 22 SE-171 48 Solna, Sweden
Re-labelling and supply of comparator product (Nipruss®)	Apoteket AB, Clinical Trial Unit Dag Hammarskjölds väg 18, Entrance C7 SE-751 85 Uppsala, Sweden
Electronic data capture system provider	Viedoc Technologies AB Stationsgatan 23 SE-753 40 Uppsala, Sweden

Signatures are provided in Section 19.

6 INTRODUCTION

6.1 Background

Compound 21 (C21) is a potent and selective nonpeptide angiotensin II type 2 receptor (AT_2R) agonist being developed for oral treatment of rare lung diseases where there is a substantial medical need for new therapeutic alternatives.

Although the renin-angiotensin system (RAS) is best known as a major physiological regulator of blood pressure and fluid homeostasis, several other physiological functions including cell growth and differentiation, cell adhesion, inflammation and fibrosis are also regulated by the RAS. Angiotensin II (Ang II) is the major effector peptide of the RAS system.

Ang II has potent vasoconstrictor effects mediated by the angiotensin II type 1 receptor (AT_1R) [1]. The AT_2R is described as a central component of the "protective arm" of the renin-angiotensin system [2]. In a study consisting of infusion of drugs into the brachial artery and measuring the response to forearm vasculature, Ang II infusion caused a dose dependent vasoconstriction; AT_2R inhibition with PD-123319 (AT_2 receptor blocker) increased the vasoconstriction response, indicating a vasodilatory role of the receptor [3].

Intra-arterial (i.a.) infusion of an AT_2R agonist (not C21) has previously been tested in healthy volunteers and was shown to cause vasodilation in the forearm [4]. Further, the AT_2R contributed to Ang II-mediated vasodilation in resistance arteries of hypertensive diabetic patients treated with AT_1R blocker [5].

In a pre-clinical study on human heart micro-coronaries, it was demonstrated that endothelial cells expressed the AT_2R, and that exposure to C21 caused relaxation of the vessels mediated through nitric oxide (NO) [6]. AT_2R stimulation in human endothelial cells increases endothelial nitric oxide synthase (eNOS) activity through phosphorylation of activating eNOS residues and dephosphorylation of inactivating eNOS residues, thus increasing NO release [7].

6.2 Non-clinical data

C21 exerts antifibrotic effects in several *in vivo* and *in vitro* models of fibrosis. In both the bleomycin -and monocrotaline-induced rat models of pulmonary fibrosis, C21 attenuated pulmonary fibrosis and within the monocrotaline model, C21 also reversed it. In addition, C21 restored cardiac function and reduced pulmonary vascular remodelling and pulmonary hypertension. The antifibrotic effects were in several studies accompanied by anti-inflammatory as well as antiproliferative effects. In the Sugen-Hypoxia (SuHx) model of pulmonary hypertension, C21 caused a robust reduction of the SuHx-induced increase in endothelial cell hyperplasia and pulmonary hypertension.

[redacted]

[redacted]

[redacted]

More detailed information is found in the current version of the C21 Investigator's Brochure (IB) [8].

6.3 Clinical experience

The efficacy of oral C21 in subjects with coronavirus disease 2019 (COVID-19) has been investigated in a multicentre, randomised, placebo-controlled, double-blind phase 2 clinical study (VP-C21-006). The subjects were randomised to receive oral treatment with C21 (100 mg twice daily, n=51) or placebo (n=55) for 7 days on top of standard of care (SoC). The study results show that oral C21 on top of SoC, including glucocorticoids and Remdesivir, was beneficial in the treatment of COVID-19, where subjects receiving C21 had a significantly lower risk for extended need of supplementary oxygen therapy.

The safety and tolerability of C21 have been evaluated in three completed phase 1 studies (C21-001-16, C21-002-16, and C21-003) and in the above mentioned completed phase 2 study (VP-C21-006) with a total of 134 subjects exposed to at least one dose of C21. The phase 1 studies involved single ascending doses and multiple ascending doses of up to 200 mg C21 twice daily administered for up to 8 days in healthy subjects and daily doses of 100 mg C21 administered for 8 days in obese subjects. The phase 2 study involved 100 mg C21 twice daily (200 mg daily dose) administered for 7 consecutive days in subjects with COVID-19.

Two phase 2 studies are currently ongoing; VP-C21-004 in subjects with Raynaud's phenomenon secondary to systemic sclerosis to show proof of mechanism of C21 on vasodilation (12 subjects; dosing has been completed), and VP-C21-005 in subjects with idiopathic pulmonary fibrosis to evaluate safety, tolerability, pharmacokinetics, and efficacy of C21 in idiopathic pulmonary fibrosis.

[redacted]

[redacted]

In the phase 2 study in subjects with COVID-19 (VP-C21-006), the majority of TEAEs were of mild or moderate severity and no TEAE was considered related to treatment by the Investigator. The most frequently reported TEAE was a minor increase in blood glucose with a higher incidence in the C21 group compared to placebo. The vast majority of events were of mild severity and none of the events were related to treatment, considered by the Investigator. Four fatal SAEs were reported after treatment in the completed phase 2 study (VP-C21-006). Two subjects died following COVID-19 infection leading to cardio-respiratory arrest, 1 in the C21 group and 1 in the placebo group. Two further subjects in the placebo group died as a result of COVID-19-related pneumonia. None of the events was judged related to treatment with C21 by the Investigator and all events were considered consistent with COVID-19.

[redacted]

Sodium nitroprusside at low doses has been used frequently in a similar brachial artery model in previous experimental studies with no safety issues observed [9, 10, 11].

6.4 Venous occlusion plethysmography

Venous occlusion plethysmography has been used extensively to study human vascular physiology *in vivo*, including i.a. drug administration. In fact, forearm venous occlusion plethysmography with local brachial artery infusion has become one of the golden standards in the assessment of vascular function in health and disease, and an accurate, reproducible and convenient method to assess the effect of new vasoactive drugs and hormones in humans *in vivo*. The advantage of the plethysmography technique is that drugs can be given at doses 10 to 100 times below those causing systemic effects because forearm blood flow (FBF) (<50 mL/min) is around 100-fold lower than cardiac output. Therefore, the effects on resistance vessels can be studied without invoking systemic effects or neurohormonal reflexes, minimising the potential for side-effects and toxicity [11].

6.5 Study rationale

With the nonclinical and clinical observed efficacy and safety profile, C21 has the potential as a beneficial therapeutic agent for patients with fibrotic lung diseases.

The rationale for conducting this phase 1 study is to provide further insight into the physiology/pharmacology of AT_2R agonists and their relevance to disease, and to provide a method to assess the dose-dependent vasodilatory response of AT_2R agonists. Hence, data from this study will serve to guide and support design of further clinical studies of new AT_2R agonists. The rationale for the study design is presented in Section 8.2.

6.6 Risk/benefit assessment

The healthy subjects participating in this study will have no medical benefit from participation and their safety and wellbeing are of outmost importance.

The FBF (<50 mL/min) is around 100-fold lower than cardiac output and by using venous occlusion plethysmography, investigational medicinal product (IMP) can be infused locally at doses 10 to 100 times lower than those causing systemic effects. The low dose range will minimise the potential for side-effects and toxicity [11].

There is extensive world-wide experience of using local brachial artery infusions of vasoactive agents, and it is considered a safe technique. Benjamin et al. have performed more than 1,000 such experiments, with no significant adverse effects [12].

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.

The Principal Investigator at the study site will ascertain that adequate facilities and procedures are available to handle emergency situations should they occur during the study. The medical staff at CTC have extensive experience from early phase 1 studies and there are adequate procedures in place to handle unexpected and expected adverse reactions in the study subjects.

A comprehensive non-clinical and early clinical data package is available for C21, as [redacted] With the total dose of C21 in the current study being 1.715 mg, safety margins for systemic exposure based on non-clinical data are extensive, [redacted]

The potential local toxicity risks related to the new administration route applied in the current study are discussed in Section 6.6.2. The excipients of the new formulation to be used are all well-known and accepted for use in injectable formulations.

Since there are no data available on reproductive toxicology for C21, only male subjects will be recruited. Each subject will be provided with a subject information card with information about the subject's participation in a study, see Section 14.4.

Besides the risks related to the test product C21, as described in Sections 6.2 and 6.3, there may also be risks related to the medical devices used in the study. Venous blood sampling and arterial catheter placement may be associated with mild-to-moderate pain, haematoma, inflammation, bleeding, bruising, or infection at the puncture site. However, when these devices are used by trained staff, the risk associated with their use is considered low and ethically justifiable.

6.6.1 Risks associated with arterial cannulation

Arterial cannulation will be performed by a trained physician according to standard hospital procedures (see Section 11.2.1). The risk of accidental extravascular infusion is assessed as minimal. Backflow of blood will be checked before infusion and saline will be infused to verify correct placement.

The subjects will be lying still in bed during the treatment with the arm in the same position and the risk of dislocation during the treatment period is considered minimal.

In case of accidental extravascular infusion, no local toxicity is anticipated due to the low concentrations infused (see Section 6.6.2). Also due to the continuous wash-out by the flowing blood in combination with the short half-life of C21, no accumulation of C21 to the tissue is expected.

In very rare instances, insertion of arterial catheters may cause blocking of the artery, tearing of the artery, arterial leakage, poor healing, or infection at the insertion site [13]. To mitigate such risks, the cannula used will be small, the puncture will be done with a stylet rather than by using a guidewire and a Seldinger technique. Further, the duration of the FBF assessment procedure is short, which limits the risk of infection.

After removal of the catheter a compression bandage will be applied to prevent bleeding. Written instructions regarding how to handle the bandage, how to manage symptoms and when to contact the Investigator will be provided to the subject before leaving the clinic.

6.6.2 Risks related to local tolerance

The risk for local tissue irritability by C21 in this model has been thoroughly assessed and it has been concluded that a dedicated nonclinical local tolerance study is deemed not to be needed. This reasoning is based on:

1. The general safety findings generated in nonclinical and clinical studies with C21 [8].

2. The daily doses to be used in this small exploratory study are between 100 to 300 times below the established safe oral human doses. Hence, the initial total dose given i.a. will be a microdose of 15 µg C21 and the maximal dose will be 1 mg (total daily dose 1.715 mg). For comparison, the established safe single human therapeutic oral dose is 200 mg.
3. The highest concentration of C21 that will be infused into the arterial blood is 100 µg/mL, and with an infusion rate of 2 mL/min, the temporary local intravascular concentration of C21 is estimated, including potential variance in the local blood flow, to be significantly below 10 µg/mL, which can be compared to the mean systemic C_{max} of 230 µg/mL achieved in monkeys without any safety concerns [8]. As a comparison, the systemic mean systemic C_{max} after a single oral 200 mg dose is approximately 4.5 µg/mL.
4. The study design is following a careful dose escalation strategy, which allows timely risk mitigation to take place. Thus, any potential reactions at the infusion site will be closely monitored by the Investigator and any signs of tissue irritability or pain will be promptly detected (the subjects are awake) and the infusion can be discontinued if deemed necessary.

6.6.3 Risk assessment with regards to the COVID-19 pandemic

Current recommendations from the authorities will be considered on a day-to-day basis. Assessment sessions with Sponsors, Investigators, and contract research organisation (CRO)/vendor representative members to align on local restrictions, impact assessment, contingency plans and study-specific risk mitigation strategies will be made to safeguard the study conduct and the safety of the subjects included in the study. Risks regarding subject safety, study performance and data quality/integrity will hence be assessed on an ongoing basis during the study. The risks and mitigating actions will be documented in a risk log as part of the Sponsor's trial master file (TMF).

European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 pandemic as well as local guidelines from the Swedish Medical Products Agency have been taken into consideration. Planned prevention and mitigating actions are outlined in Table 6.6-1. Risks and mitigating actions will be updated as applicable over the course of the study.

This study has a short in-person time frame including a healthy population. Hence, study participation is not expected to confer increased risks to the subjects in terms of COVID-19 exposure.

Table 6.6-1 COVID-19 related risks and mitigating actions

Risks identified	Actions
Subjects may be exposed to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may lead to subsequent development of COVID-19.	In accordance with recommendations by the Public Health Agency of Sweden (Folkhälsomyndigheten), subjects are not allowed to visit the clinic if they have any symptoms that may be COVID-19-related, as assessed by the Investigator. Subjects will be reminded about the restrictions by a text message, that will be sent to the subjects prior to each visit. The absence of COVID-19-like symptoms will also be verified in association with site entry.
	COVID-19 Ag rapid tests (Humasis) for detection of the SARS-CoV-2 nucleocapsid and the SARS-CoV-2 spike receptor binding domain from nasal swabs might be performed in participating subjects when arriving to study visits. Testing will be used in the study as long as it is indicated due to the spread of SARS-CoV-2 in the community. The performance and the result of each test will be documented in the subject's medical records. If a subject tests positive, the subject will be sent home and the event will be reported as an AE. Rapid testing will be performed as needed based on the prevailing COVID-19 situation at the time of study conduct as judged by the Investigator. Rapid testing will not be performed at screening visits or at visits with a shorter duration, such as follow-up visits.
	Adjustments will be made at the research clinic so that an acceptable physical distance can be maintained between the subjects
	The subjects will be recommended not to use public transport to and from the clinic.
	Subjects will be supplied with hand disinfectants to be used during clinic visits.
	Subjects will be supplied with hand disinfectants to be used during clinic visits.
	All door and drawer handle and basins at the sites will be disinfected each day.
Subjects may get ill between visits and will therefore not be able to come to the clinic site for study assessments within allowed time windows.	AEs and compliance will be followed up by phone calls.
	Subjects with suspected Covid-19 symptoms will be asked to seek SARS- CoV-2 testing.
	Subjects who test positive for COVID-19 between visits will be referred to standard hospital care if needed.
Subjects may get ill with Covid-19-like symptoms during a visit.	There is a clear action plan if a subject becomes ill during the site visit. The subject will be isolated and unless unwarranted for safety reasons, the subject will be sent home, and carefully followed up with phone calls by site staff. If the subject cannot be sent home due to safety reasons, the subject will be isolated and site staff who are in contact with the subject have to wear protective clothing and equipment. The Principal Investigator or delegate will contact the nearest infection clinic and decide on further actions.
The hospital laboratory may not be able to analyse safety samples due to the number of COVID-19 samples.	An accredited lab has been contracted as a back-up lab for analysis of safety samples.

Risks identified	Actions
New recommended actions by health authorities, such as society lock-down if the pandemic escalates, which will cause a halt in the study.	This risk does not affect subject safety.
On-site monitoring is not possible to perform in accordance with the monitoring plan due to the Covid-19 outbreak and entry restrictions to the site.	Remote centralised monitoring activities will be increased as will centralised review of data.
Increased number of protocol deviations due to the Covid-19 outbreak.	All protocol deviations will be documented and handled according to the CTU's standard operating procedures (SOPs).

6.6.4 Risk-benefit conclusion

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

More detailed information about the known and expected benefits and risks, and reasonably expected adverse reactions of C21 is found in the current version of the C21 IB [8].

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary objective

The primary objective is to investigate the effect of C21 on FBF measured by strain-gauge venous occlusion plethysmography in healthy male subjects.

7.1.1 Primary endpoint

The primary endpoint is percent change from baseline in FBF, in response to increasing i.a. doses of C21.

7.2 Secondary objectives

The secondary objectives are:

- To establish the dose-response curve for C21.
- To explore the method of measuring FBF by strain-gauge venous occlusion plethysmography by using sodium nitroprusside as a positive control.
- To evaluate safety and tolerability of i.a. administrations of C21 to healthy male subjects.

7.2.1 Secondary endpoints

The secondary endpoints are:

- Dose-response curve of C21.
- Percent change from baseline in FBF, in response to increasing i.a. doses of sodium nitroprusside.
- Frequency, intensity and seriousness of AEs.
- Clinically significant changes in vital signs, ECG and safety laboratory parameters.

8 STUDY DESIGN

8.1 Overall study design and schedule of events

This is a phase 1, open-label, single-centre study investigating the effects of i.a. infusions of the AT_2R agonist C21 on FBF in 5 healthy male subjects, by use of strain-gauge venous occlusion plethysmography.

Consenting subjects will be screened for eligibility according to study-specific eligibility criteria (see Sections 9.4 and 9.5) within 30 days prior to IMP administration (Visit 1; screening).

Eligible subjects will be scheduled for a treatment visit (Visit 2; Day 1). Relevant inclusion/exclusion criteria will be confirmed and a standardised meal (breakfast or lunch depending on the time of the day) will be served 60 minutes (min) prior to the first FBF measurement.

Measurements of FBF will be performed using a Conformité Européenne (CE)-marked automated strain-gauge venous occlusion plethysmography equipment providing on-line measurements, following a pre-specified procedure (see Section 11.2.1).

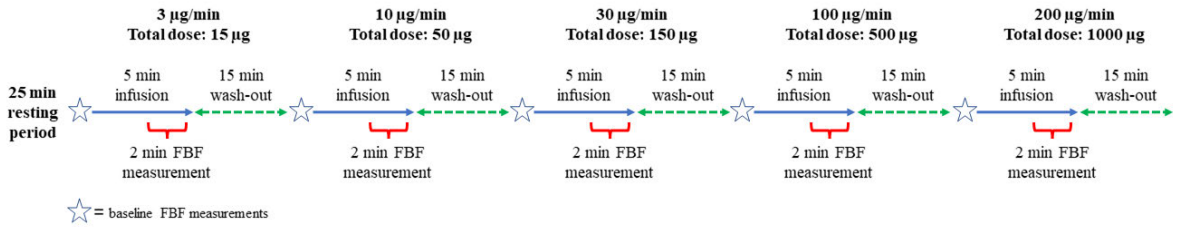
The subjects will be placed resting in a comfortable supine position in a quiet room with normal room temperature (+20 to +25º C) [14] with the forearms positioned above the level of the heart. Cuffs will be placed on the widest part of both forearms and a smaller cuff will be placed around each wrist. The non-infused arm is used as a contemporaneous control to account for any minor changes in FBF affecting both arms, *e.g.* emotional stress or temperature changes.

A catheter will be inserted into the brachial artery of the nondominant arm following standard hospital procedures (see Section 11.2.1) and a resting period of approximately 25 min will follow. At the end of this resting period, baseline measurements of FBF will be performed.

Ascending doses of C21 (3, 10, 30 100 and 200 µg/min) will be administered through local i.a. infusions for 5 min/dose with an infusion rate of 1 mL/min or 2 mL/min for the 200 µg/min dose. Measurements of FBF will be performed in both arms simultaneously during the last 2 min of each infusion/dose. The C21 doses will be separated by a wash-out period of at least 15 min. At the end of each wash-out period FBF will be measured and a baseline value for the next dose will be recorded. The Investigator will assess any emerging AEs by subject interview between each dose before deciding to proceed to the next dose level.

A flow-chart of the C21 dosing and FBF measurement schedule is presented in Figure 8.1-1.

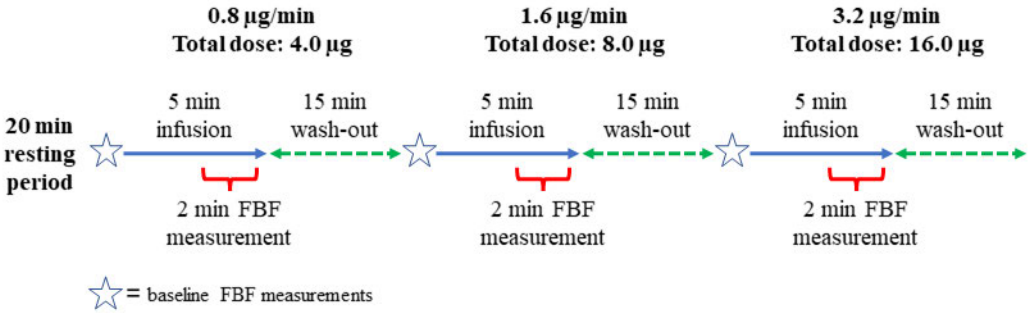
Figure 8.1-1 Dosing and measurement flow-chart for C21 infusions



When the last C21 dose has been administered there will be a resting period of 20 min. At the end of this resting period, FBF will be measured and a baseline value for the first sodium nitroprusside dose will be recorded.

Infusions of sodium nitroprusside solution (Nipruss®) will be performed as a positive control, using the same methodology as described above. Ascending doses of 0.8, 1.6, and 3.2 µg/min will be administered. A flow-chart of the Nipruss® dosing and FBF measurement schedule is presented in Figure 8.1-2.

Figure 8.1-2 Dosing and measurement flow-chart for Nipruss® infusions



Safety assessments (blood pressure, pulse, ECG, and safety laboratory parameters) will be performed prior to first dose of IMP and before the subject leaves the clinic. Any occurrence of AEs during the procedure will be recorded.

After removal of the arterial catheter a compression bandage will be applied to prevent bleeding. Written instructions regarding how to handle the bandage, how to manage symptoms and when and how to contact the Investigator if necessary, will be provided to the subject before leaving the clinic.

A follow-up phone call (end-of-study) will be performed 7 to 10 days after the treatment visit (Visit 2).

The schedule of events is shown in Table 8.1-1. Study assessments are described in Section 11.

Table 8.1-1 Schedule of events

		Screening	Treatment	End-of-study
Visit/contact	**Refer to CSP section:**	**Visit 1**	**Visit 2**	**Follow-up call**
Assessment		Day -30 to Day -1	Day 1	Day 8 to Day 11
Informed consent	14.3	X		
Inclusion/exclusion criteria	9.4, 9.5	X	X[1]	
Demographics	11.1.3	X		
Weight, height, BMI	11.1.4	X		
Medical/surgical history	11.1.5	X		
HIV, hepatitis B and C	11.1.6	X		
Alcohol test	11.1.7	X	X	
Urine drug screen	11.1.8	X	X	
Physical examination	11.1.9	X		
Clinical laboratory profile[2]	11.3.4	X	X[3]	
Vital signs (blood pressure and pulse)	11.3.2	X	X[3]	
12-lead safety ECG	11.3.3	X	X[3]	
Standardised breakfast/lunch	9.6.1		X[4]	
IMP administration	10.5		X	
FBF measurements (plethysmography)	11.2.1		X[5]	
Baseline symptoms	11.1.11	X	X[6]	
Adverse events	11.3.1		X[7]	X
Prior and concomitant medications	11.1.10	X	X	X

1. Confirmation of relevant inclusion/exclusion criteria.
2. Clinical chemistry, haematology and coagulation.
3. Before first IMP administration and before leaving the clinic.
4. Served 60 min prior to first FBF measurement.
5. For detailed procedures and timepoints, see Section 11.2.1.
6. Until start of study procedure on Day 1.
7. From start of study procedure on Day 1.

8.2 Rationale for study design

This study evaluates for the first time the dose-response related vasodilative effects of C21.

Suggested dose escalation design and i.a. infusion has been widely used in the FBF design for the past 80 years contributing to exploring human vascular physiology in vivo [11] and is considered as a golden standard in the assessment of vascular function.

Strain-gauge venous occlusion plethysmography will be use as a method for assessment of the primary endpoint (see Section 6.4).

The study design involves careful monitoring of the subject's well-being. Furthermore, by infusing IMP locally, drug-induced changes in blood pressure and cardiovascular reflexes can be minimised.

8.2.1 Selection of starting dose and rationale for planned dose escalation

The pre-defined doses of C21 (3, 10, 30, 100 and 200 µg/min) have been selected to achieve sufficient coverage of the receptor during the plethysmography measurements. The required dose of C21 to produce a local effect in the forearm is estimated based on prior similar studies [4]. The maximum dose of 200 µg/min has been chosen to ensure that a full dose-response curve is achieved. The total dose at the 200 µg/min dose level will not exceed 1 mg (see Section 10.5, Table 10.5-1). Overall, C21 was well tolerated at doses up to 100 mg twice daily administered for up to 8 days [8].

Sodium nitroprusside is selected as a positive control due to its potent vasodilative properties. The doses of Nipruss® (sodium nitroprusside) (0.8, 1.6, and 3.2 µg/min) have been selected to achieve vasodilative effects demonstrated in previous experimental studies [9, 10]. The total dose at the highest dose level will not exceed 16.0 µg (see Section 10.5, Table 10.5-2).

9 STUDY POPULATION

Prospective approval of protocol deviations from eligibility criteria, also known as protocol waivers or exemptions, will not be permitted.

9.1 Recruitment

The subjects will be recruited from CTC's database of healthy volunteers and/or through advertisement in social media.

9.2 Screening and enrolment log

Investigators must keep a record of all subjects screened even if they were not subsequently included in the study. 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 (Visit 1). 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 study.

Subjects included will be assigned a subject number (*e.g.* 101, 102 etc).

If a subject cannot receive the planned doses of IMP within 30 days after screening (*i.e.* the time interval between signing informed consent until IMP administration), the subject should be re-screened before being included in the study.

9.3 Number of subjects

Approximately 10 subjects will be screened to achieve 5 included and evaluable subjects. For replacements of subjects who discontinue from the study, see Section 9.8.4.

9.4 Inclusion criteria

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

1. Willing and able to give written informed consent for participation in the study and to comply with study requirements.
2. Healthy male subject aged 18-45 years inclusive at the time of signing the informed consent.
3. Body mass index (BMI) $\geq$ 18.5 and $\leq$ 30.0 kg/m^2.
4. 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 4 weeks after dosing with the IMP. Their female partner of child-bearing potential must use 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 4 weeks after last dose).

5. Clinically normal medical history, physical findings, vital signs, ECG and laboratory values at the time of screening, as judged by the Investigator.

9.5 Exclusion criteria

Subjects must not enter the study 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 study, or influence the results or the subject's ability to participate in the study.
2. History of thrombotic disease, vascular disorder, or severe bleeding disease.
3. Poor brachial artery access.
4. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of Day 1 (Visit 2).
5. Malignancy within the past 5 years with the exception of basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
6. Any planned major surgery within the duration of the study.
7. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus (HIV).
8. After 10 min supine rest at the time of screening, any vital signs values outside the following ranges:
    - Systolic blood pressure <100 or >140 mmHg, or
    - Diastolic blood pressure <50 or >90 mmHg, or
    - Pulse <45 or >90 beats per minute (bpm)
9. Prolonged QTcF (>450 ms), cardiac arrhythmias or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the Investigator.
10. 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 the IMPs, including any of the excipients of the IMPs.
11. Regular use of any prescribed or non-prescribed medication including antacids, analgesics, herbal remedies, vitamins, and minerals within 2 weeks prior to Day 1 (Visit 2), at the discretion of the Investigator.
12. Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) within 2 weeks prior to Day 1 (Visit 2).
13. Vaccination within 1 week prior to dosing or plans to receive any vaccine during the study conduct.
14. Planned treatment or treatment with another investigational drug within 3 months prior to Day 1 (Visit 2). Subjects consented and screened but not dosed in previous phase 1 studies are not excluded.

15. Current regular smokers or users of nicotine products. Irregular use of nicotine (*e.g.* smoking, snuffing, chewing tobacco) less than 3 times per week is allowed before the screening visit.
16. History of alcohol abuse or excessive intake of alcohol, as judged by the Investigator.
17. Presence or history of drug abuse, as judged by the Investigator.
18. Positive screen for drugs of abuse or alcohol at screening or Day 1 (Visit 2), prior to administration of the IMP.
19. History of, or current use of, anabolic steroids.
20. Inability to refrain from consuming caffeine-containing beverages during Day 1 (Visit 2), *e.g.* propensity to develop headaches when refraining from caffeine-containing beverages.
21. Plasma donation within 1 month of screening or blood donation (or corresponding blood loss) during the 3 months prior to screening.
22. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements.

9.6 Restrictions during the study

The subjects must be willing to comply with the following restrictions during the entire study duration *i.e.* from screening to the end-of-study contact.

9.6.1 General restrictions

- Contraception Requirements: The male subjects are expected to use condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of dosing until 4 weeks after last dose of the IMP. Fertile female partners are expected to use contraceptive methods with a failure rate of < 1% to prevent pregnancy (for details, refer to inclusion criterion no. 4).
- Meals: A standardised breakfast or lunch, depending on the time of the day, will be served to all subjects 60 min prior to the first FBF measurement.
- Alcohol: Consumption of alcohol is not allowed within 48 hours prior to screening (Visit 1) and Day 1 (Visit 2).
- Drugs of abuse: Use of drugs of abuse is not allowed during the study (from the screening visit to the end-of-study contact).
- Coffee: No coffee or caffeine-containing drinks are allowed on Day 1 (Visit 2), until leaving the clinic. Subjects may be served caffeine free coffee.
- Xanthine or taurine containing products/beverages: Energy drinks (*e.g.* Red Bull) are not allowed on Day 1 (Visit 2), until leaving the clinic.
- Nicotine: Smoking or use of nicotine-containing products is not allowed from screening until end of Day 1 (Visit 2).
- Grapefruit and grapefruit containing products: Consumption of grapefruit and/or grapefruit containing products or Seville oranges is not allowed during the study.
- Exercise: The subjects must refrain from strenuous exercise (defined as greater than 70% of the maximal pulse rate for 1 hour or more) for 24 hours before Day 1 (Visit 2).

- Blood donation: The subjects must not donate blood or plasma during the study until 3 months after the last dose of IMP.
- Participation in other clinical studies: Study subjects are not allowed to participate in any other interventional clinical study during the study period.

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 (Day 1) until the end-of-study contact, at the discretion of the Investigator.

Any use of prescribed or non-prescribed medication including NSAIDS/ASA, antacids, analgesics, herbal remedies, vitamin supplements and minerals from the first administration of IMP (Day 1) until the end-of study contact is not allowed, except as detailed below.

Allowed medication

- Paracetamol in doses up to 2,000 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.

Other medications considered necessary for the subject´s safety and wellbeing may be given at the discretion of the Investigator during the study period. Following consultation with the Sponsor, the Investigator will determine whether the subject should continue in the study.

9.7 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical study but do not fulfil all eligibility criteria and are not subsequently included in the study. 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 once/subject if any of the following were reasons for screening failure or non-inclusion (as judged by the Investigator):

- Practical reasons
- Non-significant medical conditions (*e.g.* influenza, nasopharyngitis)
- 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 study 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 discontinued from the study at any time at the discretion of the Investigator. Reasons for discontinuation include:

- Subject decision
- Severe non-compliance to clinical study protocol (CSP) 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

9.8.2 Withdrawal in case of extravascular cannulation

In case of accidental extravascular infusion of C21 or Nipruss® the subject will be withdrawn from further infusions.

9.8.3 Procedures for discontinuation of a subject from the study

A subject who prematurely discontinues participation in the study 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 is willing, as soon as possible, to be assessed according to the procedures scheduled for the end-of-study contact. 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.

9.8.4 Subject replacement

Subjects who discontinue prior to IMP administration may be replaced. Subjects who discontinue after initiation of IMP administration, for other reason than occurrence of an AE assessed as related to the IMP, may be replaced.

9.9 Randomisation and blinding

Randomisation will not be used. This is an open-label study and all subjects will receive the same IMP and undergo the same study procedures.

10 TREATMENTS

10.1 Identity of investigational medicinal products

10.1.1 Test product

C21 is a novel first in class selective AT_2R agonist. Activation of AT_2R causes dilatation of blood vessels and inhibition of inflammation, apoptosis, and fibrosis, and is thus considered to play a beneficial counter-regulatory role to the effects of AT_1R activation.

C21 solution for local i.a. infusion will be provided in concentrations of 30 µg/mL and 100 µg/mL. These concentrations will be diluted with 0.9% saline to achieve the two lower doses (see Section 10.5).

More detailed information about the IMP composition can be found in the Investigational Medical Product Dossier.

10.1.2 Comparator product

A positive control solution will be prepared from Nipruss® powder for solution (active ingredient sodium nitroprusside dihydrate) due to the potent vasodilative properties of sodium nitroprusside.

Nipruss® is provided as a pink hygroscopic powder in amber glass ampoules. Each ampoule contains 60 mg sodium nitroprusside dihydrate powder corresponding to 53 g water free sodium nitroprusside.

The powder will be dissolved in water for injection solutions or in a 5% glucose solution. This concentrated solution will be diluted with a 5% glucose solution to achieve the doses given in Section 10.5.

10.2 Manufacturing, packaging, and labelling and release

The C21 solution will be manufactured, packed, and labelled by Ardena, Mariakerke, Belgium. The primary packaging for the bulk solution is 10 mL vials: 20 x 30 µg/mL and 30 x100 µg/mL. The vials will be packaged in an outer cartoon (secondary package). The IMP will be released and shipped to site by ClinStorage AB, Solna, Sweden.

Nipruss® powder for solution, 60 mg/ampoule, will be ordered from and labelled for the clinical study by Apoteket AB, Clinical Trial Unit, Uppsala, Sweden.

Labels will comply with applicable Good Manufacturing Practice (GMP), with Annex 13 of the European Union Good Manufacturing Practice regulations and local regulatory requirements [15].

10.3 Conditions for storage

The C21 solution should be stored refrigerated at +5º C (+2 ºC to +8 ºC).

The Nipruss® powder should be stored at room temperature (+15 ºC to +25 ºC) protected from light. The prepared solution must be protected from light by using coloured or covered tubes and syringes. The prepared solution should be used immediately following preparation. Storage of the prepared solution for a maximum of 8 hours in +2 ºC to +8 ºC is allowed, if needed.

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

10.4 Preparation and accountability

Preparation of IMPs will be done by qualified personnel, *i.e.* a site pharmacist or a registered nurse, in a dedicated room at CTC. Detailed instructions for the preparation and handling of the C21/Nipruss® solutions will be described in a separate *IMP Handling Instruction*.

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

10.5 Treatment administration

The IMP solutions will be infused through a catheter placed in the brachial artery of the non-dominant arm using standard hospital procedures for arterial cannulation.

Ascending doses of C21 (3, 10, 30, 100 and 200 µg/min) will be administered to each subject with an infusion rate of 1 mL/min or 2 mL/min for the 200 µg/min dose. Each infusion will last for 5 min. The C21 doses will be separated by a wash-out period of at least 15 min.

For the lower doses (3 µg/mL and 10 µg/min) the 30 µg/mL and 100 µg/mL solutions will be diluted 1:10 with 0.9% saline.

The doses of C21 are displayed in Table 10.5-1.

Table 10.5-1 C21 doses

Dose (µg/min)	Infusion rate (mL/min)	Concentration (µg/mL)	Infusion time (min)	Total dose (µg)
3	1	3	5	15
10	1	10	5	50
30	1	30	5	150
100	1	100	5	500
200	2	100	5	1,000

Following a 20 min resting period after the last C21 dose, i.a. infusions of sodium nitroprusside solution (Nipruss®) will be administered as a positive control. Ascending doses of 0.8, 1.6, and 3.2 µg/min will be administered at an infusion rate of 1 mL/min. Each infusion will last for 5 min. The doses will be separated by a wash-out period of at least 15 min.

The doses of sodium nitroprusside are displayed in Table 10.5-2.

Table 10.5-2 Sodium nitroprusside doses

Dose (ug/min)	Infusion rate (mL/min)	Concentration (ug/mL)	Infusion time (min)	Total dose (ug)
0.8	1	0.8	5	4.0
1.6	1	1.6	5	8.0
3.2	1	3.2	5	16.0

10.6 Continuation of treatment with investigational medicinal product

This is a phase 1 study in healthy subjects who will have no medical benefit from the treatment and thus there will be no treatment with C21 after end of study participation.

10.7 Treatment compliance

All IMP will be administered at the study site under medical supervision to ensure compliance. Dose information will be available in the eCRF.

10.8 Return and destruction of investigational medicinal products

Any unused IMP will be returned to the Sponsor or Sponsor delegate for destruction or destroyed at CTC after approval from Sponsor. All empty vials will be destroyed at the site upon confirmation from the Sponsor. The Monitor will perform final IMP accountability reconciliation at the study end to verify that all unused IMP will be adequately destroyed and documented.

11 STUDY ASSESSMENTS

The study assessments are described in the sections below and the timing of these assessments are detailed in the schedule of events (Section 8.1, Table 8.1-1).

11.1 Recording of data

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

11.1.1 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.

11.1.2 Eligibility criteria

Eligibility criteria should be checked during screening and relevant criteria confirmed before IMP administration on Day 1. The criteria are specified in Sections 9.4 and 9.5.

11.1.3 Demographic information

The following demographic data will be recorded: gender, age, dominant/non-dominant arm, ethnicity, and race.

11.1.4 Weight and height

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

11.1.5 Medical/surgical history

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

11.1.6 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 study. Any positive result will exclude the subject from participating.

11.1.7 Alcohol test

An alcohol test will be performed at time points outlined in the schedule of events (Table 8.1-1).

11.1.8 Urine drug screen

Urine will be screened for drugs of abuse at time points outlined in the schedule of events (Table 8.1-1) using the Drug Screen Multi-12/15 (Nal von minden).

11.1.9 Physical examination

A complete physical examination will be performed at screening and will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities.

Any abnormalities will be specified and documented as clinically significant or not clinically significant.

11.1.10 Prior and concomitant medications

Information on prior medications taken within 2 weeks prior to screening will be obtained by subject interview to verify that the eligibility criteria are met (see also Section 9.6.2).

Medications will be classified as prior if treatment is discontinued before the first IMP administration and as concomitant if ongoing at the time of the first IMP administration, stopped after the first IMP administration or started after the first IMP administration. To distinguish between prior and concomitant medications on Day 1 (*i.e.* the 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 prior/concomitant medications from screening (Visit 1) until the last end-of-study contact 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.

11.1.11 Baseline symptoms

A baseline symptom is defined as a medical event that occurs between the subject's signing of the ICF until initiation of the study procedures on Day 1 (*i.e.* an event that occurs during the screening period). Such events are not AEs and will be recorded as baseline symptoms in the Medical History Log in the eCRF.

11.2 Efficacy assessments

11.2.1 Strain-gauge venous occlusion plethysmography

Measurements of FBF will be performed using a CE-marked automated strain-gauge venous occlusion plethysmography equipment providing on-line measurements; Bergenheim, Elektromedicin, Göteborg, Sweden.

The underlying principle of this method is that when the venous return from the forearm is briefly interrupted by inflating a cuff placed around the upper arm to well above venous pressure but below diastolic pressure, and arterial inflow continues unimpeded, the forearm swells at a rate proportional to the rate of arterial inflow. Changes in forearm volume result in a corresponding change in arm circumference and thus strain-gauge length, which can be detected as an alteration in electrical resistance of the gauge, and thus potential difference [16].

The subject will be placed resting in a comfortable supine position in a quiet room with normal room temperature (+20 ºC to +25 ºC) [14]. Both forearms must be positioned above the level of the heart to ensure adequate venous emptying during the period of deflation. This position will be achieved by resting the elbows on foam pads and supporting the hands with pillows. Cuffs will be placed on the widest part of both forearms and a smaller cuff will be placed around each wrist. The non-infused arm is used as a contemporaneous control to account for any minor changes in FBF affecting both arms, *e.g.* emotional stress or temperature changes.

A catheter will be inserted into the brachial artery of the nondominant arm according to standard hospital procedures. A standard arterial cannula will be used. The artery will be palpated at the elbow of the non-dominant arm. The skin will be cleaned with alcohol after which the artery is cannulated transcutaneously. A small infusion of saline will be connected to maintain the line opened.

After cannulation there will be a resting period of approximately 25 min. At the end of this resting period, baseline measurements of FBF will be performed.

The subject will receive ascending doses of C21 (3, 10, 30, 100 and 200 µg/min) through local i.a. infusions for 5 min/dose with an infusion rate of 1 mL/min or 2 mL/min for the 200 µg/min dose. The start -and stop times of the infusions will be recorded. Measurements of FBF will be performed in both arms simultaneously during the last 2 min of each infusion. The C21 doses will be separated by a wash-out period of at least 15 min. At the end of each wash-out period FBF will be measured and a baseline value for the next dose be recorded.

For each FBF measurement, an inflation pressure of 60 mmHg will be used for intervals of approximately 7 sec followed by approximately 8 sec of deflation. This cycle will be repeated approximately 8 times during the last 2 min of each infusion. The wrist cuff will be inflated to supra-systolic pressures within 30 sec before each measurement to exclude the hand circulation. Changes in forearm volume will be measured using strain-gauges placed around the widest part of the forearms. A measure of blood flow to that part of the forearm enclosed by the two cuffs is provided, expressed as mL per 100 mL of forearm volume per minute. Actual forearm volume can be estimated by calculation, assuming the forearm is a simple truncated cone, or by simple water displacement.

When the last C21 dose has been administered, the infusion will be discontinued and there will be a resting period of 20 min. At the end of this resting period, FBF will be measured and a baseline value for the first sodium nitroprusside dose will be recorded.

Infusions of sodium nitroprusside solution (Nipruss®) will be performed as a positive control, using the same methodology as described above. Ascending doses of 0.8, 1.6, and 3.2 µg/min will be administered.

After removal of the arterial catheter a compression bandage will be applied to prevent bleeding.

11.3 Safety assessments

11.3.1 Adverse events

The Principal Investigator is responsible for ensuring that all medical staff involved in the study is familiar with the content of this section and the content of the CTC SOPs regarding emergencies and phase 1 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 product. 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-patient 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 reaction

The term adverse reaction is to be used whenever either the Investigator or Sponsor or designee assessed the AE as related to the IMP.

11.3.1.4 Definition of serious adverse 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 suspected unexpected serious adverse reaction (SUSAR) is any SAR whose nature or intensity is not consistent with the current reference safety information (RSI) in the IB or summary of product characteristics (SmPC) and therefore, is assessed as unexpected.

11.3.1.6 Time period and frequency for collecting adverse events

All AEs (including SAEs) will be collected from the start of the study procedure on Day 1 until the end-of-study contact. Any AE with start date on Day 1 must be recorded with start time.

During the end-of-study contact, 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 study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

11.3.1.7 Assessment of intensity

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

Mild	Awareness of symptoms, sign, illness, or event that is easily tolerated.
Moderate	Discomfort sufficient to cause interference with usual activity.
Severe	Incapacitating with inability to work or undertake further normal activities.

11.3.1.8 Assessment of causal relationship

The Investigator must assess the causal relationship between an AE and the IMPs (C21 and Nipruss® will be assessed separately) using the definitions below and record it on the AE Log of the eCRF:

Related	There is a reasonable possibility that the AE was caused by the IMP. There is a reasonable time relationship to IMP administration. 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.

Causality to study procedures will also be assessed.

11.3.1.9 Assessment of outcome

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

0 =	**Unknown**	
1 =	**Recovered/resolved**	The subject has recovered completely, and no symptoms remain.
2 =	**Recovering/resolving**	The subject's condition is improving, but symptoms still remain.
3 =	**Not recovered/not resolved/ongoing**	The subject's condition has not improved, and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
4 =	**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).
5 =	**Fatal**	

11.3.1.10 Reporting of action taken with study treatment

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

Dose not changed

Drug interrupted

Drug withdrawn

Not applicable

Unknown

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

Adverse events 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.

Adverse events, 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

Serious adverse event reporting should be performed by the Investigator within 24 hours of awareness using the paper SAE form, provided in the investigator site file (ISF). All available information regarding the SAE should be entered using the SAE form (*i.e.* term, intensity, causality, outcome, SAE criteria, action taken, narrative including rational for causality assessment) for the specific subject. The completed, signed and dated paper SAE Form should, within 24 hours, be scanned and e-mailed to:

Email: Vicore@primevigilance.com

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 Vicore@primevigilance.com. However, all SAE management and follow-up takes place via the SAE paper forms.

The SAE report is reviewed by a designated person at PrimeVigilance 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 PrimeVigilance 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. Such follow-up information should be documented on a new SAE report form, marked as a follow-up report and emailed to Vicore@primevigilance.com.

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

The Sponsor or delegate will assume responsibility for reporting SAEs to the competent authority (CA) and independent ethics committee (IEC) in accordance with local regulations.

11.3.1.14 Expedited reporting of suspected unexpected serious adverse reaction

The term SAR is used whenever either the Investigator or Sponsor deems an SAE related to the IMP. If an SAR is assessed as unexpected it will be reported as a SUSAR to the CA and to the IEC in accordance with local regulations within the following timelines:

- 7 calendar days if fatal or life-threatening (follow-up information within an additional 8 days)
- 15 calendar days if non-fatal and non-life-threatening (follow-up information as soon as possible)

11.3.1.15 Treatment and follow-up of adverse events

Subjects with AEs occurring during the study must be treated according to daily clinical practice at the discretion of the Investigator.

Adverse events must be followed up until resolution or to the end-of-study contact, whichever comes first. At the end-of-study contact, 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-study contact 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 recovered, stabilised, or recovered with sequelae, 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 the pregnancy (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even after the end of the subject's study 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 in this CSP.

Over-dosing is not likely to occur in this study since the IMPs will be administered by site personnel under medical surveillance. The doses to be administered are substantially lower than the doses considered well tolerated in clinical practice (Nipruss®) and based on previous clinical studies (C21).

In cases of accidental overdose of C21, standard supportive measures should be adopted as required. No known antidote is available.

In cases of accidental overdose of sodium nitroprusside (Nipruss®), standard supportive measures should be adopted as required. Overdosage of sodium nitroprusside can be manifested as excessive hypotension or cyanide toxicity or as thiocyanate toxicity.

Treatment of cyanide toxicity: Acidosis may not appear until more than an hour after the appearance of dangerous cyanide levels, and laboratory tests should not be awaited. Reasonable suspicion of cyanide toxicity is adequate grounds for initiation of treatment.

Treatment of cyanide toxicity consists of:

- discontinuing the administration of sodium nitroprusside;
- providing a buffer for cyanide by using sodium nitrite to convert as much haemoglobin into methaemoglobin as the patient can safely tolerate; and then
- infusing sodium thiosulfate in sufficient quantity to convert the cyanide into thiocyanate

The necessary medications for this treatment are contained in commercially available Cyanide Antidote Kits.

Any 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 only reported in the subject's medical records and on the protocol deviation log.

11.3.2 Vital signs

Systolic and diastolic blood pressure and pulse will be measured in supine position after 10 min of rest at time-points specified in Table 8.1-1.

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

11.3.3 Electrocardiogram

Single 12-lead ECG will be recorded in supine position after 10 min of rest using an ECG machine at time-points specified in Table 8.1-1. Heart rate and PR, QRS, QT and QTcF intervals will be recorded. 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 by the Investigator. Abnormal post-dose findings assessed as clinically significant will be reported as AEs.

11.3.4 Laboratory safety assessments

Blood samples for analysis of clinical chemistry, haematology and coagulation parameters will be collected through venepuncture or an indwelling venous catheter at time-points specified in Table 8.1-1 and sent to the certified Clinical Chemistry and Pharmacology laboratory at Uppsala University Hospital and analysed by routine analytical methods. The safety laboratory parameters are defined in Table 11.3-1.

Any lab values outside the normal ranges will be judged as not clinically significant or clinically significant by the Investigator. The assessment will be recorded in the eCRF. Abnormal post-dose values assessed as clinically significant will be reported as AEs. If an abnormal value is associated with corresponding clinical signs or symptoms, the sign/symptom should be reported as the AE.

Table 11.3-1 Safety laboratory parameters

Category	Parameter
Clinical chemistry	Alanine aminotransferase (ALT)
	Albumin
	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
	Bilirubin (total and conjugated)
	Blood urea nitrogen (BUN)
	Calcium
	Creatinine (estimated glomerular filtration rate [eGFR] included)
	Glucose
	Potassium
	Sodium
Haematology (MCHC)	Haematocrit (erythrocyte volume fraction [EVF])
	Haemoglobin (Hb)
	Mean corpuscular volume (MCV)
	Mean corpuscular haemoglobin (MCH)
	Mean corpuscular haemoglobin concentration (MCHC)
	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])

11.4 Appropriateness of measurements

Strain-gauge venous occlusion plethysmography has been commonly used during the past 80 years and is considered a golden standard in the assessment in vascular function.

All methods used for safety assessments are commonly used in standard medical care and in phase 1 clinical studies.

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

Safety laboratory samples will be collected according to standard procedures.

12.2 Volume of blood

The anticipated volume of blood samples collected during the study 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
Clinical chemistry, haematology, coagulation	3	20 mL	60 mL
HIV, Hepatitis B/C	1	4 mL	4 mL
Total			**64 mL**

12.3 Handling, storage, and destruction of laboratory samples

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

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 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 the study site 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 study site, are immediately identified, disposed of/destroyed and the action is documented.

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

13 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Quality management: critical process, system, and data identification

During CSP development, the Sponsor have identified those processes, systems (facilities, computerised systems) and data that are critical to ensure human subject protection and the reliability of study results according to applicable SOPs and International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH) E6 R2.

Identified risks are categorised separately from the CSP. Risks associated with the COVID-19 pandemic and mitigation actions are described in Table 6.6-1. Sponsor oversight responsibilities, such as monitoring, AE reporting, safety monitoring, changes in Investigators and key study team staff and quality assurance activities may need to be reassessed in relation to the COVID-19 pandemic and temporary, alternative proportionate mechanisms of oversight may be required. An updated risk assessment will be performed prior to enrolment of the first subject.

13.2 Quality assurance and quality control

The Sponsor has implemented and is responsible for quality assurance (QA) and quality control (QC) systems with written SOPs with regards to management of identified risks, CSP compliance, good clinical practice (GCP) compliance and applicable regulatory requirements for all parties involved in the study.

The Sponsor is responsible for securing agreements with involved vendors and to perform regular vendor oversight to ensure CSP compliance, GCP compliance and compliance with applicable regulatory requirements.

Quality control is 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 study oversight of any study-related duties and functions carried out on its behalf. All references to Sponsor also apply to CTC with regards to the study related duties and functions carried out by CTC on Sponsor’s behalf. CTC must therefore implement both QA and QC.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [17] and are consistent with ICH/GCP E6 (R2), EU Clinical Trials Directive, and applicable local regulatory requirements.

14.2 Ethics and regulatory review

The Principal Investigator is responsible for submission of the CSP, 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 has delegated to CTC the responsibility to submit study documents to the applicable CA 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 Investigator 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 study subject adequate verbal and written information before any study specific assessments are performed.

The information will include the objectives and the procedures of the study as well as any risks or inconveniences involved. It will be emphasised that participation in the study 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 study and will be given sufficient time to consider participation before signing the ICF.

Before performing any study-related procedures the ICF must be signed and personally dated by the subject and 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 must 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 information card

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

- That he is participating in a clinical study

- Subject study ID
- That he will be/has been dosed 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 General Data protection Regulation (GDPR EU 2016/679), the data will be pseudonymised and not directly identify any persons taking part in the study.

The potential study subject should be informed that by signing the ICF he approves that authorised representatives from Sponsor and CTC, the concerned IEC and CA have direct access to his medical records for verification of clinical study 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 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.

If the subject withdraw his consent to the collection, use and disclosure of information, no new information will be collected for the purposes of this study. However, data collected before withdrawal will be used as part of the study material.

The Investigator must file a *Subject Identification List* which includes sufficient information to link records, *i.e.* the eCRF and clinical records. This list will 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 study 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 study. After the study end, only pseudonymised data, *i.e.* aggregated data sets, can be used.

For this study, the Sponsor is the data controller of all data processed during the study (*e.g.* TMF, clinical study report [CSR]) and CTC is the data processor. Any subcontractors used in the study, are also data processors.

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

14.6 Changes to the approved clinical study protocol

Any proposed change to the approved final CSP will be documented in a written and numbered CSP amendment. All substantial amendments to the CSP 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 the IEC may perform audits or inspections at the study site, with permission from the Investigator to have direct access to source data/documents. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the CSP, ICH-GCP guidelines, GDPR and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a CA about an inspection at the study site.

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 STUDY MANAGEMENT

15.1 Training of study site personnel

Before enrolment of the first subject, a Sponsor representative or delegate will perform a study initiation visit at the study site. The requirements of the CSP and related documents will be reviewed and discussed, and the investigational staff will be trained in any study-specific procedures and systems utilised.

It is the responsibility of the Principal Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study 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 study must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the study together with their function and study-related duties delegated. A Curriculum Vitae will be available for all staff to whom study-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 study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign CAs.

As defined in the risk-based monitoring (RBM) plan, approved by the Sponsor and provided separately, the responsible Monitor will periodically visit the study 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 (see Table 6.6-1). Results of adjusted monitoring/review measures should be reported to the Sponsor in monitoring reports and in the CSR. 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 CSP, applicable SOPs, guidelines, manuals, and regulatory requirements
- 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
- verify that the correct informed consent procedure has been adhered to for participating subjects
- 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 CSP
- 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 study team members at CTC in accordance with the RBM plan.

When the study 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 the study 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 study. 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 Study agreements

The Principal Investigator must comply with all the terms, conditions, and obligations of the *Clinical Study Agreement* for this study.

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

15.5 Study timetable and end of study

The study is expected to be performed in Q1 2022.

A subject is considered to have completed the study if he has completed all study visits and contacts including the end-of-study phone call.

The end of the clinical part of the study is defined as the end-of-study phone call of the last subject participating in the study.

15.6 Termination of the study

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

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study or potential study subjects; 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 study, the CA can suspend or prohibit the study. 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 study is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the subjects and should assure appropriate follow-up for the subjects.

15.7 Reporting and publication

15.7.1 Clinical Study Report

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

A CSR, in compliance with ICH-E3, describing the conduct of the study, 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 study results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the study.

15.7.2 Annual safety report

If the study duration exceeds 1 year, the Sponsor must submit a 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 study.

15.7.3 Confidentiality and ownership of study data

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

15.7.4 Publication

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

15.8 Archiving

Records and documents pertaining to the conduct of this study should be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. This includes any original source documents related to the study, the *Subject Identification List* (providing the sole link between named subject source records and pseudonymous 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 (including metadata, audit trail and closed queries) will be sent to the Sponsor and a copy will be retained at the clinic and filed in the ISF for archiving for 25 years after finalisation of the CSR.

The completed eCRFs are the 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 CSP.

Data validation/data cleaning procedures are designed to assure validity and integrity of the 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 and data listing for data quality reviews on data exports. All study-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 processes will be described in a study-specific *Data Management Plan*.

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 study site before inclusion of the first subject (Section 15.3).

Authorised site personnel designated by the Investigator will complete data collection. Appropriate eCRF training and security measures for access control will be completed with the Investigator and all authorised site personnel prior to the study being initiated and any data being entered into the system for any study 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 study 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 during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations.

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, according to the RBM plan. 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. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF.

If corrections are needed, queries will be raised within the eCRF, either because 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, readable, and not editable 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 (*i.e.* safety laboratory data and FBF data). Data may be received in electronic format or as a paper printout.
Key variables are defined to uniquely identify each sample record. File and data formats are agreed with the external data provider.

Reconciliation of external data versus eCRF data will be performed ensuring data integrity.

16.6 Medical coding

Medical coding will be performed by trained personnel at CTC. Medical/surgical history verbatim terms and AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA; latest version available at start of eCRF set up). Prior and concomitant medications will be coded according to the World Health Organisation (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, discrepancies resolved, SDV has been performed according to the RBM plan, all external data and SAEs have been successfully reconciled, all medical terms have been coded, all protocol deviations have been categorised, and all Principal Investigator signatures have been collected, clean file will be declared after the classification of the subjects to the analysis populations, the database will be locked, and the data will be ready for analysis.

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*, 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, standard deviation (SD), median, minimum, and maximum value. Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment (test product/comparator), and by assessment time. Individual subject data will be listed by subject number, treatment, 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).

Baseline for the safety assessments will be defined as the last data collection point prior to the first administration of IMP. For the FBF measurements, a baseline will be defined for each dose level.

No imputation of missing data will be performed.

17.2 Determination of sample size

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

Approximately 10 subjects will be screened to achieve 5 included and evaluable subjects.

17.3 Analysis data sets

17.3.1 Full analysis set

The full analysis set (FAS) will consist of all subjects who have been included and received at least one dose of IMP and have at least one post-baseline assessment.

17.3.2 Safety analysis set

The safety analysis set will compromise all subject who received at least one dose of the IMP.

17.4 Description of study population

17.4.1 Demographics and baseline characteristics

Descriptive statistics for demographics, weight, height, BMI, and dominant/non-dominant arm will be presented.

Individual data will be listed by subject.

17.4.2 Medical/surgical history and prior/concomitant medication

Medical/surgical history will be summarised by system organ class (SOC) and preferred term (PT). Prior/concomitant medications will be presented by ATC level 4 and 5.

Individual data will be listed by subject.

17.4.3 Physical examination

Clinically significant and non-clinically significant abnormal findings will be specified and presented by subject.

Individual data will be listed by subject.

17.4.4 Treatment compliance

The number of subjects administered each IMP and start and stop times for each infusion will be listed.

17.5 Analysis of efficacy endpoints

17.5.1 Effect of C21 on forearm blood flow

The response to increasing i.a. doses of C21 will be summarised using descriptive statistics with percent change from baseline and presented by dose.

17.5.2 Dose-response

The dose response curve of C21 will be presented using a mixed model. The natural logarithm of the maximum FBF value for each dose level and each subject will be used as the dependent variable in the model. Dose will be used as a class variable and subject as a random variable. Kenward-Roger's approximation for degrees of freedom will be used. The least square means (LSMeans) estimates for the doses will be presented in a plot. In addition, the pairwise LSMeans differences between the doses will be tabulated.

17.5.3 Effect of sodium nitroprusside on forearm blood flow

The response to increasing i.a. doses of sodium nitroprusside will be summarised using descriptive statistics with percent change from baseline and presented by dose.

17.6 Analysis of safety endpoints

17.6.1 Adverse events

An overview of all AEs, including SAEs, intensity, relationship to IMP/study procedures, and deaths will be presented by treatment group. Incidence of AEs and SAEs will be summarised by SOC and PT.

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

17.6.2 Vital signs

Vital signs (systolic/diastolic blood pressure and pulse) will be summarised using descriptive statistics. Data will be presented with absolute change from baseline.

Individual data will be listed by subject.

17.6.3 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 using descriptive statistics.

Individual data will be listed by subject.

17.6.4 Safety laboratory analyses

Safety laboratory data will be summarised using descriptive statistics with absolute change from baseline. Abnormal, clinically significant values will be summarised separately, if considered appropriate.

Individual data will be listed by subject.

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19.2 Signature page (approval of the clinical study protocol)

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