CLINICAL STUDY PROTOCOL

Prospective, open-label, single arm, multicenter pharmacokinetic, and safety study of a single dose intravenous human plasma-derived C1 Esterase Inhibitor (C1-INH) concentrate in patients with congenital C1-INH deficiency and hereditary angioedema

Investigational Product:	Human plasma-derived C1 esterase inhibitor, OCTA-C1-INH
Indication:	Hereditary angioedema type I and type II
Study Design:	Prospective, open-label, single arm, multicenter, pharmacokinetic, and safety study
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Straße 235 1100 Vienna, Austria
Study Number:	CONE-01
EudraCT and/or IND Number:	2019-001693-28
Development Phase:	Phase ~~2a~~ 1
Planned Clinical Start:	Q4 2019
Planned Clinical End:	Q3 2020
Date of Protocol:	~~01-Aug-2019~~30-Jan-2020
Version:	090-CSP-CONE-01-**V02.2**
Co-ordinating Investigator:	Dr. med. Inmaculada Martinez-Saguer Hämophilie-Zentrum Rhein Main GmbH Hessenring 13a 64546 Mörfelden-Walldorf Germany

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STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H., 1100 Vienna, Austria	
Name of Investigational Product: OCTA-C1-INH	**Protocol Identification Code:** CONE-01
Name of Active Ingredient: C1 Esterase Inhibitor (plasma-derived, human)	**Date of Final Protocol:** ~~01-Aug-2019~~30-Jan-2020

Title of Study:

Prospective, open-label, single arm, multicenter, pharmacokinetic, and safety study of a single dose intravenous human plasma-derived C1 Esterase Inhibitor (C1-INH) concentrate in patients with congenital C1-INH deficiency and hereditary angioedema

Indication:

Hereditary angioedema (HAE) type I and type II

Number of Study Sites:

10 study sites

Objectives:

Primary Objective:

- The primary objective of this study is to assess the pharmacokinetic (PK) characteristics of OCTA-C1-INH after a single intravenous (IV) administration in HAE patients who are not experiencing an HAE attack.

Secondary Objectives:

The secondary objectives of this study are:

- To assess blood level changes of C1-INH antigen and C4 level after a single IV administration of OCTA-C1-INH.
- To assess the safety of OCTA-C1-INH IV administration.

Study Design:

Prospective, open-label, single arm, multicenter, phase ~~2a~~ 1 study.

The study design follows the conventions for PK investigations. Twenty patients with HAE type I or type II will receive 1 single dose of OCTA-C1-INH treatment.

Mandatory hospitalization for patient observation during and after administration of OCTA-C1-INH is required for 24 hours (from day 0 to day 1 for study visits 2 and 3). Hospitalization beyond the 24 hours period is recommended and can be done according to local clinical practice.

Patients will be enrolled in the study when they are not having an HAE attack. In the event a patient has an HAE attack anytime during the study before PK sampling is completed,

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standard of care treatment will be applied, and the patient will be discontinued from the study. In the event a patient has an HAE attack anytime during the study after PK sampling is completed, standard of care treatment will be applied, and the patient will be continued in the study for follow-up. If a patient has an HAE attack during the (pre-)screening period or before injection of the investigational medicinal product (IMP), the patient may be re-screened once he/she fulfills the eligibility criteria again.

Since this is the first study of OCTA-C1-INH, there will be an independent data monitoring committee (IDMC) to review the aggregated safety data after treatment of the first 6 patients enrolled in the study. Enrollment will be stopped after the 6th patient and only be allowed again after the IDMC recommendation to proceed. Pre-screening of new patients will be allowed while the IDMC decision is pending.

Number of Patients:

20 planned patients

Patient Selection Criteria:

Male and female patients with HAE type I or type II

Inclusion Criteria:

1. Documented congenital C1-INH deficiency with C1-INH functional activity less than 50% and C4 level below the laboratory reference range.
2. Age ≥18 years at informed consent date.
3. Signed informed consent.
4. Patient must be capable to understand and comply with the relevant aspects of the study protocol.
5. Women of childbearing potential must have a negative pregnancy test at screening as well as pre-infusion and must agree to use acceptable methods of contraception from screening until final visit. Refer to Section 4.2.3 for further details.
6. Fertile male patients must agree to use acceptable methods of contraception from screening until final visit. Refer to Section 4.2.3 for further details.

Exclusion Criteria:

1. Any signs of an HAE attack OR HAE attack within 7 days prior to dosing with the IMP (OCTA-C1-INH) OR more than a total of 9 HAE attacks over the previous 3 months prior to dosing with the IMP.

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2. Patients who have received prophylactic or acute treatment with C1-INH (Berinert®, Cinryze®, HAEgarda®, Ruconest®, etc.), non-biological bradykinin pathway inhibitors (e.g., ecallantide, icatibant), or treatment with tranexamic acid within 2 weeks prior to dosing with the IMP.
3. Patients who have received treatment with lanadelumab within 11 weeks prior to dosing with the IMP.
4. Patients with planned dental, medical, or surgical procedures who will need pre-procedural HAE prophylaxis during the study period.
5. Female patients taking estrogen-containing contraceptive regimen, hormone replacement therapy (excepting progesterone-only contraceptives, which are permitted), or selective estrogen receptor modulators (e.g., tamoxifen). Male patients on specific androgen therapy (e.g., testosterone, danazol, dehydroepiandrosterone/androstenedione).
6. Any change (start, stop, or change in dose) in androgen therapy (e.g., oxandrolone, stanozolol) in the last 14 days prior to dosing with the IMP.
7. Participated in any other investigational drug evaluation or received blood or a blood product, except for C1-INH, within 30 days prior to dosing with the IMP.
8. Live viral vaccination within 30 days prior to screening.
9. Acute infectious illness characterized by rapid onset of disease, a relatively brief period of symptoms, and resolution within a short period of time.
10. Risk factors for thromboembolic events, including presence of indwelling venous catheter or access device, history of thrombosis, underlying atherosclerosis, morbid obesity (defined as BMI of ≥35 kg/m^2 and experiencing obesity-related health conditions or ≥40 to 44.9 kg/m^2), immobility, or medications known to increase thromboembolic risk.
11. History of allergic reaction to C1-INH products or other blood products.
12. History of clinically relevant antibody development against C1-INH.
13. Any history of B-cell malignancy that was unresolved in the past 5 years.
14. Pregnancy or lactation.
15. Any clinically significant medical or psychiatric condition that, in the opinion of the Investigator, would interfere with the patient's ability to participate in the study.

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Test Product, Dose, and Mode of Administration:

OCTA-C1-INH 500 international units (IU), lyophilized powder to be reconstituted with 2.5 mL water for injection (WFI) at a dose of 20 IU/kg body weight.

OCTA-C1-INH will be administered by slow IV injection.

Reference Therapy, Dose, Mode of Administration,

Not applicable.

Duration of Treatment:

Patients will receive 1 single injection of the IMP (OCTA-C1-INH~~).~~) during mandatory hospitalization.

Study Outcome Parameters (Primary and Secondary Endpoints):

Pharmacokinetic Parameters:

Primary Endpoint:

The primary endpoint is the PK parameters of OCTA-C1-INH, measured as C1-INH activity.

The PK parameters that will be assessed for OCTA-C1-INH include:

- Blood concentrations at each sampling time
- Maximum blood concentration (C_{max})
- Time to maximum concentration (T_{max})
- Clearance (CL)
- Area under the concentration-time curve (AUC)
- AUC normalized by the dose (AUC_{norm})
- Mean residence time (MRT)
- Incremental recovery (IR)
- Volume of distribution (V_d)
- Elimination half-life ($T_{1/2}$)

Secondary Endpoints:

- PK parameters of the following analytes:
  - C1-INH antigen
  - C4 level

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All PK parameters determined for the primary PK endpoint will also be determined for the secondary PK endpoints.

- Safety Parameters:
  - Number and severity of adverse events (AEs)
  - Change in vital signs from pre- to post-injection
  - Change in laboratory parameters from pre- to post-injection
  - Blood nuclear antigen tests for hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]-1/2, and parvovirus B19
  - Anti-C1-INH antibodies

Study Procedures:

The duration of the entire study period for each patient will be maximum 3.5 months. It will consist of up to 2.5 months of optional pre-screening, up to 14 days of screening, administration of open-label IMP, and a 1-week PK sampling period. The final visit is scheduled 14 days (±3 days) after IMP administration.

Patients who have given their written informed consent and fulfill all inclusion criteria but do not meet any of the exclusion criteria will be included into the study. Screening investigations will be carried out (as per Table 1).

Eligible patients will be enrolled to receive 1 single dose of OCTA-C1-INH injected within 14 days after screening. Study procedures and assessments will be carried out (as per Table 1).

Patients will be monitored and carefully observed for any symptoms throughout the injection period and for 1 hour post-injection. Vital signs will be closely monitored pre-injection, once during the injection, and 30 minutes to 1 hour post-injection.

If an AE occurs during the injection, the injection will be paused, and vital signs will be measured. The injection should be restarted only if the AE subsides and the supervising clinician determines that it is safe to restart the injection. The injection should be restarted very slowly.

Adverse events and information on concomitant medications will be collected starting at day 0 (pre-injection).

Statistical Analysis Plan:

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to start of the statistical analysis.

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All collected PK and safety parameters will be listed and presented as descriptive statistics.

The following analysis sets will be considered for the statistical analysis:

Safety analysis set (SAF) consisting of all patients who received the IMP injection.

Full analysis set (FAS) is defined according to the intention-to-treat (ITT) principle and consists of all patients of the safety analysis set who satisfy all eligibility criteria and for whom any post-baseline data are available; it is the set of eligible patients with treatment effects measured.

Per-protocol (PP) set consists of all patients of the FAS excluding those with protocol deviations which may have an impact on the analysis of the primary endpoint. This is the set of patients who participated in the study as planned and for whom the primary endpoint can be evaluated as planned.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP set.

PK parameters listed as primary and secondary endpoints will be determined using non-compartmental methods.

The planned sample size is 20 patients to have 18 evaluable patients. This is considered sufficient to ensure sufficiently accurate characterization of the PK properties of OCTA-C1-INH. The mean baseline-corrected AUC of C1-INH is expected to be in the magnitude of 2000 IU×hr/mL with a corresponding coefficient of variation of about 0.35. With these assumptions, the AUC analysis would result in a 90% confidence interval with a half-width of about 286 IU×hr/mL.

The safety analysis will comprise descriptive statistics, tabulations, and listings of all treatment-emergent adverse events (TEAEs), laboratory results, viral nuclear antigens, vital signs, presence of anti-C1-INH antibodies, and physical examination findings.

All reported AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA; Version 22.0).

FLOWCHART OF ASSESSMENTS

Table 1: Flowchart of Assessments Performed Throughout the Study

ASSESSMENTS	Pre-Screening (optional)	Visit 1 (Screening Visit)	Visit 2			Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 Final Visit (planned or early discontinuation)
	Day -90 to Day -15	Day -14 to Day -1	Day 0			Day 1	Day 2	Day 3	Day 5	Day 6	Day 7	Day 14
Visit/sampling windows			Pre-injection	During injection	Post-injection	±1 hour	±2 hours	±2 hours	±2 hours	±2 hours	±2 hours	±3 days
Informed consent	X	X[1]										
Eligibility criteria (inclusion/exclusion)		X	X									
Demographic and baseline characteristics	X (age, sex)	X[1]										
Weight for dose calculation		X										
Medical history and prior medication	X	X										
Pregnancy test[2]		X (serum)	X (urine)									X (urine)
Physical examination		X			X[3]							X
Vital signs		X	X	X	X (within 30 to 60 minutes)							X
Routine safety laboratory tests[4]		X	X			X[3]						X
Viral nuclear antigen testing[5]		X										X
Enrollment			X									
Injection of IMP				X[10]								
PK sampling (C1-INH activity and C1-INH antigen concentration; C4 level)[6]	X (C1-INH activity, C4 level)		X[7]		X[8] 5 time points	X 24 hours	X 48 hours	X 72 hours	X 120 hours	X 144 hours	X 168 hours	
Hospitalization			X	X	X	X						
Anti-C1-INH antibodies[9]			X									X

Adverse event monitoring			Throughout the study
Concomitant medication			Throughout the study

Abbreviation: IMP = investigational medicinal product (OCTA-C1-INH)

[1] Pre-screened subjects have to re-consent at screening. Pre-screening assessments for age and sex do not have to be repeated at screening.

[2] This test is to be conducted only for female patients of childbearing potential.
Serum pregnancy test is to be conducted at the central laboratory, urine pregnancy test to be done locally.

[3] In the first 6 patients only.

[4] Hematology and clinical chemistry; testing to be conducted at central laboratory.

[5] Viral nuclear antigens include hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]-1/2, and parvovirus B19; testing to be conducted at central laboratory.

[6] Other extremity (arm, leg) to be used than for IMP administration; refer to the PK sample processing instructions for details.
Testing to be conducted at central laboratory.

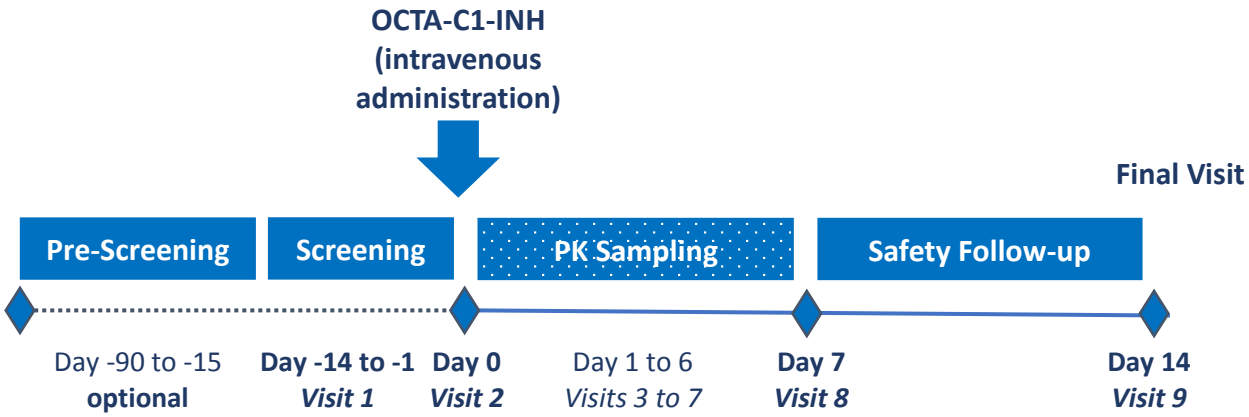
[7] A single pre-injection sample is to be taken. Pre-injection sampling window will be ≤30 minutes.

[8] Post-injection samples to be taken at 0 minutes (sampling window of +2 minutes) and 15 minutes (sampling window of ±2 minutes); at 1 hour and 6 hours (sampling window of ±5 minutes); and at 12 hours (sampling window of ±10 minutes).

[9] Testing to be conducted at central laboratory.

[10] All patients will be monitored and carefully observed for any symptoms for at least 1 hour post-injection.

Figure 1: Study Scheme



Abbreviations: PK=pharmacokinetic

PROTOCOL SIGNATURES

Signatures of the Sponsor's Representatives

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

Dr. Wolfgang Frenzel

International Medical Director Signature Date
on behalf of the Sponsor
Octapharma Pharmazeutika Produktionsges.m.b.H
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Mag. Vera Bürger

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PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

Dr. Inmaculada Martinez-Saguer

Coordinating Investigator Signature Date

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under the Concentration-Time Curve
AUC_{norm}	Area Under the Concentration-Time Curve Normalized by the Dose
BMI	Body Mass Index
C1-INH	Complement 1-Esterase Inhibitor
CL	Clearance
C_{max}	Maximum Blood Concentration
CRO	Contract Research Organization
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
HAE	Hereditary Angioedema
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IR	Incremental Recovery (defined as Cmax-Cpredose/Dose per kg)
IRB	Institutional Review Board
ITT	Intention-To-Treat
IU	International Units
IUD	Intrauterine Device
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
PK	Pharmacokinetic
PP	Per-Protocol
RNA	Ribonucleic Acid
SAE	Serious Adverse Event

SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SDV	Source Data Verification
$T_{1/2}$	Elimination Half-Life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to Maximum Blood Concentration
V_d	Volume of Distribution
WFI	Water for Injection

GLOSSARY OF TERMS AND TRADEMARKS

Berinert®	CSL Behring
Cinryze®	Shire
HAEgarda®	CSL Behring
Phoenix® WinNonlin®	Certara
Ruconest®	Pharming

1 INTRODUCTION

Hereditary angioedema (HAE) is a rare disorder characterized by attacks of edema formation affecting different parts of the body. Subcutaneous edema typically affects the face, hands, arms, legs, or genitals. Swelling of abdominal organs could cause diarrhea, vomiting, and severe pain and may mimic surgical emergency potentially leading to operation. Laryngeal involvement can lead to death by asphyxiation[1].

The condition is inherited with an autosomal dominant trait, but spontaneous mutations also occur at conception. Three different types of HAE have been described. Type I HAE is the most common form and is caused by decreased production of Complement 1 Esterase Inhibitor (C1-INH). In type II HAE, the amount of C1-INH in the blood is not decreased but the functionality of the molecule is impaired. In another variant of HAE (type III) with uncertain pathophysiology, the C1-INH levels and function are normal. These three different types of HAE are characterized by the same symptoms[2,17].

The treatment of HAE patients has two main aspects. Depending on the frequency of attacks, the patients might need long-term or intermittent prophylaxis. In case of an HAE attack, administration of drugs may be needed to reduce the severity and the duration of the symptoms. Depending on the availability of the drugs and considering possible side-effects, antifibrinolytic agents (e.g., ε-aminocaproic acid, tranexamic acid), synthetic attenuated androgens (e.g., danazol, stanozolol), plasma-derived C1-INHs, and bradykinin pathway inhibition are used for prophylaxis. For treatment of acute attacks, plasma-derived or recombinant C1-INHs, kallikrein antagonists or bradykinin antagonists are used where available. These specific treatment options are not accessible in every country and to every patient in the different countries. When specific medications are not available, fresh frozen plasma is used occasionally to increase C1-INH level in the blood, but this treatment has variable efficacy. Depending on the condition of the patient, additional measures are also used in the management of HAE attacks: fluid replacement in case of hypotension, narcotics for severe pain, intubation or tracheostomy in case of airway compromise.

Plasma-derived C1-INH products are already available in the market. C1-INH replacement therapy with human plasma-derived C1-INH concentrate is an effective and well tolerated treatment for acute attacks of HAE[3].

Currently, there are few commercially available plasma-derived and recombinant IV C1-INH products – in Europe for treatment of acute attacks Berinert® (CSL Behring[4]) and the recombinant human C1-INH Ruconest® (Pharming[5]), and Cinryze® (Shire[6]) which is also approved for prophylaxis.

In the US, Berinert® (CSL Behring[7]) and the recombinant human C1-INH Ruconest® (Pharming[8]) for treatment of acute attacks, Cinryze® (Shire[9]), and the subcutaneous C1-INH HAEgarda® (CSL Behring) for prophylaxis are commercially available.

1.1 Rationale for Conducting the Study

Plasma-derived C1-INHs are widely used in the management of HAE type I and type II patients, both for on-demand treatment and for prophylaxis. Clinical studies conducted with intravenous (IV) administration of plasma-derived C1-INH products showed clear benefit in comparison to placebo[10,11].

Following regulatory requirements, safety and efficacy of OCTA-C1-INH will have to be demonstrated. The rationale for this study is to investigate the pharmacokinetic (PK) properties and safety profile of OCTA-C1-INH in patients during an attack-free period. Introducing OCTA-C1-INH to the market will help in meeting the needs of HAE patients.

In approximately 50% of cases, HAE manifestations first occur in childhood. Clinical manifestation of HAE usually begins at the age of 5-11 years[12], although there is often a delay in HAE diagnosis until teenage years or even adulthood[13,14,15].

The study will be conducted in compliance with the protocol, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)-Good Clinical Practice (GCP), and other regulatory requirements.

1.2 Dose Rationale

The present study aims to investigate the PK of OCTA-C1-INH and to demonstrate safety.

Intravenous administration of an established, branded C1-INH product at a dose of 20 international units (IU)/kg body weight has been shown to be generally well tolerated in the marketed dose range.

1.3 Benefit-Risk Statement

The present study is the first one with OCTA-C1-INH. The aim of this study is to investigate the PK properties and the safety profile of OCTA-C1-INH in HAE patients during an attack-free period. Similar types of adverse reactions are expected to be observed with marketed plasma-derived C1-INH medicinal products. Efficacy is not being evaluated in this study.

There will be an independent data monitoring committee (IDMC) review of the aggregated safety data of the first 6 patients enrolled in the study. The IDMC will then decide whether it is safe to continue dosing for the remaining patients.

OCTA-C1-INH is a stable, virus-inactivated, highly-purified concentrate of human C1-INH. It is prepared from human blood, and therefore transmission of infectious agents cannot be totally excluded. Specific virus inactivation procedures are implemented in the manufacturing process of OCTA-C1-INH which are described in detail in the Investigator's Brochure (IB)[16].

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the PK characteristics of OCTA-C1-INH after a single IV administration in HAE patients who are not experiencing an HAE attack.

2.2 Secondary Objective

The secondary objectives of this study are:

- To assess blood level changes of C1-INH antigen and C4 level after a single IV administration of OCTA-C1-INH.
- To assess the safety of OCTA-C1-INH IV administration.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary endpoint is the PK parameters of OCTA-C1-INH, measured as C1-INH activity.

The PK parameters that will be assessed for OCTA-C1-INH include:

- Blood concentrations at each sampling time
- Maximum blood concentration (C_{max})
- Time to maximum concentration (T_{max})
- Clearance (CL)
- Area under the concentration-time curve (AUC)
- AUC normalized by the dose (AUC_{norm})
- Mean residence time (MRT)
- Incremental recovery (IR)
- Volume of distribution (V_d)
- Elimination half-life ($T_{1/2}$)

3.1.2 Secondary Endpoints

The secondary endpoints include:

- PK parameters of the following analytes:
  - C1-INH antigen
  - C4 level

All PK parameters determined for the primary PK endpoint will also be determined for the secondary PK endpoints.

- Safety:
  - Number and severity of adverse events (AEs)
  - Change in vital signs from pre- to post-injection
  - Change in laboratory parameters from pre- to post-injection
  - Blood nuclear antigen tests for hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]-1/2, and parvovirus B19
  - Anti-C1-INH antibodies

3.2 Overall Study Design and Plan

This study is planned to start in Q4 2019 and to be clinically completed by Q3 2020. The study is a prospective, open-label, single-arm, multicenter, phase ~~2a~~ 1 study involving 20 patients, aged 18 years or older, with type I or type II HAE.

HAE is a rare disease and the number of patients required for this study is relatively high. It is therefore planned to initiate 10 study sites.

An optional pre-screening visit for confirmation of the HAE type I or type II diagnosis (inclusion criterion #1) can take place up to 90 days prior to administration of investigational medicinal product (IMP).
The entire study period will be maximum 3.5 months for a patient. It will consist of up to 2.5 months of optional pre-screening, up to 14 days of screening, administration of open-label IMP, and a 1-week PK sampling period. The final visit is scheduled 14 days (±3 days) after IMP administration.

Patients who have given their written informed consent and fulfill all inclusion criteria but do not meet any of the exclusion criteria will be included into the study. Screening investigations will be carried out (refer to Flowchart of Assessments Table 1 Table 1and Section 6.1.1).

Eligible patients will be enrolled to receive 1 single dose of OCTA-C1-INH injected within 14 days after screening. Study procedures and assessments will be carried out (refer to Flowchart of Assessments Table 1).

Patients will be monitored and carefully observed for any symptoms throughout the injection period and for 1 hour after the injection. Vital signs will be closely monitored pre-injection, once during the injection, and 30 minutes to 1 hour post-injection.

If an AE occurs during the injection, the injection will be paused, and vital signs will be measured. The injection should be restarted only if the AE subsides and the supervising clinician determines that it is safe to restart the injection. The injection should be restarted very slowly. Adverse events and information on concomitant medications will be collected throughout the study.

The study procedures that will be carried out at each visit are detailed in Section 6.1.

There will be an IDMC review of the aggregated safety data after treatment of the first 6 patients enrolled in the study. Enrollment will be stopped after the 6th patient and only be allowed again after the IDMC recommendation to proceed. Pre-screening of new patients will be allowed while the IDMC decision is pending. The IDMC review will then decide whether it is safe to continue dosing for the remaining patients. Thereafter, an ongoing quarterly review of all safety data is planned.

The flow chart of assessments, including visit and sampling windows, is given in Table 1 and details of the procedures in Section 7.

3.3 Discussion of Study Design and Choice of Control Group

3.3.1 Study Design

The study design follows the conventions for PK investigations. Twenty patients with HAE type I or type II will receive 1 single IV dose of OCTA-C1-INH treatment.

Mandatory hospitalization for patient observation during and after administration of OCTA-C1-INH is required for 24 hours (from day 0 to day 1 for study visits 2 and 3). Hospitalization beyond the 24 hours period is recommended and can be done according to local clinical practice.

Patients will be enrolled in the study when they are not having an HAE attack. In the event a patient has an HAE attack anytime during the study before PK sampling is completed, standard of care treatment will be applied, and the patient will be discontinued from the study. In the event a patient has an HAE attack anytime during the study after PK sampling is completed, standard of care treatment will be applied, and the patient will be continued in the study for follow-up. If a patient has an HAE attack during the (pre-)screening period or before injection of the IMP, the patient may be re-screened once he/she fulfills the eligibility criteria again.

3.3.2 Control Group

No control group/treatment is planned in the study.

3.3.3 Study Parameters

The therapeutic rationale of OCTA-C1-INH treatment is to supplement the patients' blood with C1-INH molecules to compensate for the decreased levels of functional C1-INH molecules in HAE patients. It is thus of central importance how much of the injected C1-INH is actually available to the patient.

The following PK parameters will be measured: OCTA-C1-INH blood concentrations at each sampling time, C_{max}, T_{max}, CL, AUC, AUC_{norm}, MRT, IR, V_d, and $T_{1/2}$.

Safety assessment will be based on analysis of AEs, laboratory tests, vital signs, and physical examinations.

4 STUDY POPULATION

4.1 Population Base

Male and female patients with HAE type I or type II.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Documented congenital C1-INH deficiency with C1-INH functional activity less than 50% and C4 level below the laboratory reference range.
2. Age ≥18 years at informed consent date.
3. Signed informed consent.
4. Patient must be capable to understand and comply with the relevant aspects of the study protocol.
5. Women of childbearing potential must have a negative pregnancy test at screening as well as pre-infusion and must agree to use acceptable methods of contraception from screening until final visit. Refer to Section 4.2.3 for further details.
6. Fertile male patients must agree to use acceptable methods of contraception from screening until final visit. Refer to Section 4.2.3 for further details.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are *not* eligible for the study:

1. Any signs of an HAE attack OR HAE attack within 7 days prior to dosing with the IMP (OCTA-C1-INH) OR more than a total of 9 HAE attacks over the previous 3 months prior to dosing with the IMP.
2. Patients who have received prophylactic or acute treatment with C1-INH (Berinert, Cinryze, HAEgarda, Ruconest®, etc.), non-biological bradykinin pathway inhibitors (e.g., ecallantide, icatibant), or treatment with tranexamic acid within 2 weeks prior to dosing with the IMP.
3. Patients who have received treatment with lanadelumab within 11 weeks prior to dosing with the IMP.
4. Patients with planned dental, medical, or surgical procedures who will need pre-procedural HAE prophylaxis during the study period.
5. Female patients taking estrogen-containing contraceptive regimen, hormone replacement therapy (excepting progesterone-only contraceptives, which are permitted), or selective estrogen receptor modulators (e.g., tamoxifen). Male patients on specific androgen therapy (e.g., testosterone, danazol, dehydroepiandrosterone/androstenedione).
6. Any change (start, stop, or change in dose) in androgen therapy (e.g., oxandrolone, stanozolol) in the last 14 days prior to dosing with the IMP.

7. Participated in any other investigational drug evaluation or received blood or a blood product, except for C1-INH, within 30 days prior to dosing with the IMP.
8. Live viral vaccination within 30 days prior to screening.
9. Acute infectious illness characterized by rapid onset of disease, a relatively brief period of symptoms, and resolution within a short period of time.
10. Risk factors for thromboembolic events, including presence of indwelling venous catheter or access device, history of thrombosis, underlying atherosclerosis, morbid obesity (defined as BMI of ≥35 kg/m^2 and experiencing obesity-related health conditions or ≥40 to 44.9 kg/m^2), immobility, or medications known to increase thromboembolic risk.
11. History of allergic reaction to C1-INH products or other blood products.
12. History of clinically relevant antibody development against C1-INH.
13. Any history of B-cell malignancy that was unresolved in the past 5 years.
14. Pregnancy or lactation.
15. Any clinically significant medical or psychiatric condition that, in the opinion of the Investigator, would interfere with the patient's ability to participate in the study.

4.2 Prior and Concomitant Therapy

Details on medications taken within 90 days prior to enrollment and any concomitant medications taken during the study must be recorded in the electronic case report form (eCRF).

4.2.1 Permitted Concomitant Therapy

Prescribed medication(s) and over the counter medications not listed as prohibited in Section 4.2.2 are allowed. In addition, progesterone-only contraceptives are permitted.

4.2.2 Prohibited Concomitant Therapy

Patients who need pre-procedural HAE attack prophylaxis for elective dental, medical, or surgical procedures should have the procedure postponed until after study completion.

If a patient has an HAE attack during the study, or requires pre-procedural (e.g., for dental surgery) prevention of an acute HAE attack, they will receive standard of care treatment.

Administration of any other blood or plasma-derived product is prohibited during the study. Treatment with any short or long-term prophylactic treatment for HAE must be avoided during the study.

Other prohibited medications are:

- Prophylactic or acute treatment with C1-INH (Berinert, Cinryze, HAEgarda, Ruconest, etc.), tranexamic acid, bradykinin pathway inhibitors (lanadelumab, ecallantide, icatibant).

- Medications that increase risk of thromboembolic disease, including estrogen-containing contraceptives and hormone replacement therapy, selective estrogen receptor modulators (e.g., tamoxifen), specific androgen therapy (e.g., testosterone, danazol, dehydroepiandrosterone/androstenedione).
- Live viral vaccination.

4.2.3 Contraception Requirements

In this study, fertile male patients and female patients who are of childbearing potential will need to adhere to acceptable methods of birth control from screening until final visit. Estrogen-containing contraceptives are not permitted.

Acceptable methods of birth control include:

- Intrauterine device (IUD; including progesterone eluting IUD)
- Bilateral tubal occlusion
- Hysterectomy and/or oophorectomy
- Vasectomized partner
- Progesterone-only contraceptives (injection, pill, implants)
- Male or female condom with or without spermicide
- Cervical cap, diaphragm, or sponge; all with spermicide
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)
- Sexual abstinence, provided it is the preferred lifestyle of the patient and not based on situational circumstances

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawals can render the study non interpretable, any unnecessary withdrawal of patients should be avoided.

Patients with consecutive moderate, severe, and/or serious treatment emergent adverse events (TEAEs) should be withdrawn from the study if the Investigator considers that further participation in the study is unsafe for these patients.

Patients with severe hypersensitivity reactions, including anaphylactic reactions, should be withdrawn from the study.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. Where possible, the final visit assessments will be performed (see Section 6.1.6). If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome. Patients who discontinue for AE-related reasons should be followed up until the AE has resolved or stabilized.

4.3.2 Patient Replacement Policy

In general, patients withdrawn from the study will not be replaced. Patients will be replaced only in case of a withdrawal proportion of 20% or more to ensure that the required minimum of patients evaluable with respect to the primary endpoint are available for analysis.

Since such a high withdrawal rate is not expected, the Sponsor and the Coordinating Investigator will consult with the IDMC, before enrollment of replacement patients.

If a patient has an HAE attack during the (pre-)screening period or before injection of the IMP, the patient may be re-screened once he/she fulfills the eligibility criteria again.

Under no circumstances are patients who have been dosed with the IMP permitted to re-enroll.

4.4 Assignment of Patients to Treatment Groups

There is only one treatment group. Patients will be enrolled to receive a single IV dose of the IMP at a dose of 20 IU/kg body weight. The Investigator will enter a unique identifier of each patient in both the eCRF and the confidential patient identification list.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and the Sponsor will decide on the further participation of the patient in this study after having discussed all relevant aspects.

4.6 Subsequent Therapy

If a patient decides to withdraw from the study or is withdrawn by the Investigator, he/she may continue with the treatment he/she has received before study participation or with another standard of care.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Characterization of Investigational Product

The IMP used in the study is OCTA-C1-INH.

The IMP (500 IU) will be supplied as a lyophilized powder for solution for injection together with a solvent (water for injection [WFI]), which should be used for the reconstitution of the IMP. The batch number(s) used will be recorded in the clinical study report.

OCTA-C1-INH is a stable, sterile, virus-inactivated, highly purified concentrate of human C1-INH. It is prepared from pooled human plasma and is available as a lyophilized powder (500 IU/vial). After reconstitution with 2.5 mL WFI, the solution can be administered as slow intravenous injection. It has a potency of 200 IU/mL C1-INH.

5.2 Packaging and Labeling

The IMP will be packed and final labeling will comply with the national requirements of each country where the study is to be conducted.

The master label is presented as a separate document.

5.3 Conditions for Storage and Use

The Investigator/authorized personnel at the site will ensure that the IMP is stored in appropriate conditions with restricted access and in compliance with national regulations.

The IMP should be protected from light, from freezing, and be stored at +2°C to +25°C (36°F to 77°F). The IMP should be warmed up to room temperature before reconstitution. The reconstituted solution should not be refrigerated or frozen. The IMP must be administered at room temperature within 8 hours of reconstitution.

5.4 Dose and Dosing Schedule

The IMP will be given as single dose of 20 IU/kg body weight. The body weight measured according to the flowchart of assessments in Table 1 will be used for calculation of the dose.

OCTA-C1-INH will be administered by slow IV injection during mandatory hospitalization.

If an AE occurs during the injection, the injection will be paused, and vital signs will be measured. The injection should be restarted only if the AE subsides and the supervising clinician determines that it is safe to restart the injection. The injection should be restarted very slowly.

5.5 Preparation and Method of Administration

The IMP will be dissolved with a 2.5 mL WFI syringe, by using a vial adapter and transferring it into the vial containing the concentrate.

After reconstitution and prior to administration of the IMP, the solution should be inspected visually for particulate matter and discoloration. The reconstituted solution should be colorless, clear, and free from visible particles. Partially used vials must be discarded.

It is recommended that the calculated IMP vials are pooled in a syringe by the pharmacist or designee. The syringe is provided for the injection. Leftovers in vials after pooling must not be used anymore and must be destroyed after completion of drug accountability.

The IMP must not be mixed with other medical products or saline.

The total volume used and time of start and end of injection will be recorded.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable as the study will be conducted in an open-label manner.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

Any IMP provided to the site will be accounted for. This includes IMP received at the site and IMP administered to patients. A Drug Inventory and Dispensing Log will be kept current by the Investigator or his/her designee, detailing the date and quantity of IMP received and administered to each patient and the remaining quantity.

The inventory and dispensing log will be available to the monitor to verify drug accountability during the study.

Unused IMP can be destroyed at the study site or returned to the Sponsor for destruction. Destruction can be initiated only after accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction.

5.7.2 Assessment of Treatment Compliance

IMP will be injected at the study site under the guidance of the Investigator or his/her designee. Injection details will be documented together with IMP batch numbers.

6 STUDY CONDUCT

The flowchart of assessments is given in Table 1. Visit and sampling windows are detailed in the flow chart (Table 1) and in Section 6.1.7.

6.1 Observations by Visit

6.1.1 Pre-Screening Visit (optional)

An optional Pre-Screening Visit (Day -90 to Day -15) for confirmation of the HAE type I or type II diagnosis (inclusion criterion #1) can take place up to 90 days prior to the administration of IMP.

The following activities/assessments will be performed:

- Obtaining voluntarily given, written (signed and dated) informed consent form before any study procedures are performed
- Demographic information on age and sex
- Medical history and prior medication
- Blood sampling for C1-INH activity, C4 level

6.1.2 Screening Visit (Visit 1)

The following assessments will be performed during the Screening Visit (Day -14 to Day -1), which should take place within 14 days prior to the administration of IMP.

- (Re-)Obtaining voluntarily given, written (signed and dated) informed consent form before any study procedures are performed. Pre-screened subjects have to re-consent.
- Inclusion and exclusion criteria
- Demographic and baseline characteristics including sex, age, ethnic origin, height and body mass index (BMI)
- Weight for IMP dose calculation
- Medical history and prior medication
- Pregnancy test (serum) for female patients of childbearing potential
- Physical examination
- Vital signs
- Blood sampling for routine safety laboratory (hematology and clinical chemistry)
- Blood sampling for viral nuclear antigen testing

The following pre-screening assessments do not have to be repeated and can be used at screening:

- Age
- Sex

6.1.3 Visit 2: Administration of Investigational Medicinal Product and Hospitalization

Visit 2 (Day 0) will be the day for the IMP injection and start of PK sampling during mandatory hospitalization. Visit 2 should take place within 14 days after the Screening Visit.

Before the injection of IMP, patients' eligibility will be re-evaluated. The following activities/assessments will be performed:

- Confirmation of inclusion criteria and exclusion criteria
- Enrollment
- Vital signs
- Blood sampling for routine safety laboratory (hematology and clinical chemistry)
- Blood sampling for pre-injection PK samples within 30 minutes before the start of the injection
- Blood sampling for anti-C1-INH antibodies
- Pregnancy test (urine) for female patients of childbearing potential.
- Monitoring of AEs
- Documentation of concomitant medication

During the injection of the IMP:

- Vital signs will be monitored once during the injection
- Monitoring of AEs
- Documentation of concomitant medication

After the end of the injection:

- In the first 6 patients enrolled in the study, a physical examination will be done within 1 hour post-injection
- All patients will be monitored and carefully observed for any symptoms for at least 1 hour after the end of the injection
- Blood sampling for PK at 0 minutes (+2 minutes), 15 minutes (± 2 minutes), 1 hour (±5 minutes), 6 hours (± 5 minutes), 12 hours (± 10 minutes) after the end of the injection
- Vital signs will be measured within 30 minutes to 1 hour post-injection
- Monitoring of AEs
- Documentation of concomitant medication

6.1.4 Visit 3 and Hospitalization

Visit 3 (Day 1) will take place the day following the injection; the following assessments will be performed during mandatory hospitalization:

- In the first 6 patients enrolled in the study, blood sampling for routine safety laboratory (hematology and clinical chemistry)
- Blood sampling for PK at 24 hours (±1 hour) after the end of the injection

- Monitoring of AEs
- Documentation of concomitant medication

Hospitalization beyond the 24 hours period is recommended and can be done according to local clinical practice.

6.1.5 Visits 4 to 8

The following assessments will be performed:

- Blood sampling for PK at:
  - 48 hours (± 2 hours) (Visit 4 – Day 2)
  - 72 hours (± 2 hours) (Visit 5 – Day 3)
  - 120 hours (± 2 hours) (Visit 6 – Day 5)
  - 144 hours (± 2 hours) (Visit 7 – Day 6)
  - 168 hours (± 2 hours) (Visit 8 – Day 7)
- Monitoring of AEs
- Documentation of concomitant medication

6.1.6 End-of-Study Visit: Final Visit (Planned or Early Discontinuation; Visit 9)

At the end of the study period, a final examination comprising the following investigations will be performed:

- Pregnancy test (urine) for female patients of childbearing potential
- Physical examination
- Vital signs
- Blood sampling for routine safety laboratory (hematology and clinical chemistry)
- Blood sampling for viral nuclear antigens
- Anti-C1-INH antibodies
- Monitoring of AEs
- Documentation of concomitant medication

Where possible, these assessments will also be performed if a patient discontinues from the study. After the Final Visit (planned or early discontinuation), the study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns require follow-up.

6.1.7 Time Windows Used in this Study, Including Tolerances

The following time windows and tolerances apply in this study:

Table 2: Time Windows Used in this Study

Time point	Time stated	Tolerance
Blood sampling[1] (pharmacokinetics)	Before IMP administration	≤30 minutes
	0 minutes after IMP administration	+2 minutes
	15 minutes after IMP administration	±2 minutes
	1 and 6 hours after IMP administration	±5 minutes
	12 hours after IMP administration	±10 minutes
	24 hours	±1 hour
	48, 72, 120, 144, and 168 hours	±2 hours
Final visit	Day 14	±3 days

[1] The PK blood sampling is to be done in another extremity (arm, leg) than the IMP administration.

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be maximum 3.5 months: up to 2.5 months of optional pre-screening, up to 14 days of screening, administration of open-label IMP, and 1-week PK sampling period. The final visit is scheduled 14 days (±3 days) after IMP administration.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the planned observation period/Final Visit (planned or early discontinuation).

The study start is expected for Q4 2019, and the estimated end of the study (last visit of last patient) is Q3 2020.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. In this event, any necessary procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) should be informed in accordance with national regulations.

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.
- The IDMC detects safety concerns following the treatment of the first 6 patients enrolled in the study.
- ≥2 severe related anaphylaxis reactions, defined as immediate, life-threatening allergic reactions, are observed, fulfilling the following criteria:
  - assessed as probably or possibly related to OCTA-C1-INH treatment by Investigator and/or Sponsor
  - confirmed by the IDMC.

NOTE: Causality assessments of suspected severe hypersensitivity reactions must be made by all involved parties (Investigator, Sponsor). The IDMC will review all SAEs and AEs of special interest (AESIs) during the study.

6.2.3.2 Early Termination at an Individual Study Site

At any time, the study can be terminated at an individual site if:

- The site cannot comply with the requirements of the protocol.
- The site cannot comply with Good Clinical Practice (GCP) standards.
- The required recruitment rate is not met.

Should the study be prematurely terminated, all study materials (completed, partially completed, and blank documents, IMP, etc.) must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

7.1.1 Demographic and Baseline Characteristics

The demographic and baseline characteristics are sex, age, ethnic origin, height, weight, and BMI.

7.1.2 Medical History and Prior/Concomitant Medications

The medical history will be obtained by interviewing the patient. Records of past diseases and treatments (e.g., hospital discharge letters) will be obtained for the study files, if available.

Prior and concomitant medications will be obtained by interview.

7.2 Pharmacokinetic Assessments

7.2.1 Assessments for Primary Pharmacokinetic Endpoint

Blood samples for PK analysis will be collected as detailed in Flowchart of Assessments Table 1. Pharmacokinetic samples will be obtained and evaluated in all patients. Blood sample collection, processing, and shipping details will be outlined in a separate laboratory manual.

Concentrations of C1-INH activity and blood C1-INH will be determined by a laboratory approved by the Sponsor.

7.2.2 Assessments for Secondary Pharmacokinetic Endpoints

Blood samples for PK analysis of C1-INH antigen and C4 level will be collected, as detailed in Flowchart of Assessments Table 1.

Pharmacokinetic samples will be obtained and evaluated in all patients. Blood sample collection, processing, and shipping details will be outlined in a separate laboratory manual.

Concentrations of C1-INH antigen and C4 level will be determined by a laboratory approved by the Sponsor.

7.3 Safety Assessments

7.3.1 Assessments for Safety Endpoints

Safety-related secondary endpoints cover systemic effects as well as local or short-term reactions associated with the IMP administrations.

All of the following drug safety information shall be collected:

- Adverse events and serious adverse events (SAEs) temporally associated with the administration of IMP (for definitions and reporting requirements, see Sections 7.3.2, 7.3.3, and 7.3.4)

- Pregnancies, drug overdose, interaction, medication error, and post-study SAEs (see Section 7.3.9)
- Change in vital signs from pre- to post-injection
- Change in laboratory parameters from pre- to post-injection
- Blood nuclear antigen tests HAV, HBV, HCV, HIV-1/2, and parvovirus B19
- Anti-C1-INH antibodies

7.3.2 Adverse Events

7.3.2.1 Definitions

- **AE:** An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP. The term AE is used to include both serious and non-serious AEs.
- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of Adverse Events

The condition of the patient will be monitored throughout the study. At each visit (scheduled or unscheduled), from day 0 (pre-injection), AEs will be elicited using a standard nonleading question such as "How have you been since the last visit/during the previous study period?". Patients will be monitored and carefully observed for any symptoms throughout the injection period and at least 1 hour after end of injection.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the medical notes and eCRF. Any AE that leads to discontinuation of the patient from the study will be followed up until the AE has resolved or stabilized. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be

recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Sections 7.3.2.3, 7.3.3, and 7.3.2.4, respectively. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed, and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present at screening will be documented as medical history. If an exacerbation in intensity or frequency (worsening) occurs after the screening visit, it will be documented as an AE.

Any AE noted after the start of IMP administration will be considered as treatment-emergent and will be documented as a TEAE.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of Adverse Events

The intensity/severity of AEs will be graded as follows:

- **Mild:** An AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities.
- **Moderate:** An AE which is sufficiently discomforting to interfere with the patient's routine activities.
- **Severe:** An AE which is incapacitating and prevents the pursuit of the patient's routine activities.

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of Adverse Events

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- **Possible:** Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A

reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.

- **Unlikely:** Reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** Events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- **Unclassified:** Reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

7.3.2.5 Classification of Adverse Drug Reactions by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the IB.
- **Unexpected:** an ADR that is not listed in the current edition of the IB or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of Adverse Events

All AEs will be followed up for 4 weeks after administration of the IMP (2 weeks of follow-up in the study, followed by 2 weeks of follow-up via telephone).

The outcome of all reported AEs must be documented as follows:

1. Recovered, resolved
2. Recovered, resolved with sequelae
3. Recovering, resolving
4. Not recovered, not resolved
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported. Events leading to death and/or deaths of unknown cause will be captured from the time of signing the informed consent to up to 4 weeks after IMP injection and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and wellbeing of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an adverse event

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

b) Investigational medicinal product-related actions taken in the event of an adverse event

- None
- Injection interrupted
- IMP withdrawn

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events

An **SAE** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (see below)
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is another important medical event

NOTE: The term 'life-threatening' refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient after the injection and that was not present prior to the injection. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.4 Serious Adverse Event Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax or email to the Sponsor or designee:

Sponsor contact details for SAE reporting:

Octapharma's Corporate Drug Safety Unit:

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Oberlaaer Strasse 235, 1100 Vienna, Austria

Fax: +43 1 61032-9949

E-mail: cdsu@octapharma.com

24 hours emergency telephone number: +43 1 40 80 500

Sponsor's designee contact details for SAE reporting:

Contact details will be communicated at the study initiation visit and placed in the Investigator Site File.

An SAE form must be completed and submitted to the Sponsor and the Sponsor's designee within 24 hours after recognition of the event.

Waivers from SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry, hospitalizations for observation during and after IMP administration (PK sampling~~,~~), or prolongations of existing hospitalizations for economic or social, but not medical, reasons. ~~Such surgeries or prolongations of hospitalizations should not be considered SAEs.~~

7.3.5 Adverse Events of Special Interest

The following AEs are defined as clinically relevant AESIs:

- Immediate hypersensitivity reactions, which may include urticaria, pruritus, tightness of the chest, hypotension, feeling of impending doom, etc.
- Thromboembolic event
- Dysgeusia

For these AESIs, the general definitions and procedures that are described in Section 7.3 apply as well. AESIs of immediate hypersensitivity reactions and thromboembolic events will be reported within 24 hours of site awareness and will use the same process as SAE reporting in order to capture comprehensive information prospectively. Premature termination criteria of the entire clinical study due to severe related anaphylaxis reactions are defined in Section 6.2.3.1. The IDMC will review all SAEs and AESIs during the study.

7.3.6 Laboratory Tests

Hematology (platelet count, hematocrit, hemoglobin, red blood cell count, white blood cell count) and clinical chemistry parameters (alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatinine, urea/blood urea nitrogen, electrolytes [sodium and potassium], albumin) will be investigated during the study at a central laboratory at the time points specified in Flowchart of Assessments Table 1and Section 6.

Presence of anti-C1-INH antibodies will be checked pre-injection and at study end at a central laboratory.

A laboratory manual detailing the procedures for the central laboratory samples will be distributed to all study sites.

The methods of determination and normal ranges for each parameter will be provided in the laboratory manual.

7.3.7 Viral Safety Tests

Blood samples will be collected to test for viral nuclear antigen (deoxyribonucleic acid [DNA]/ribonucleic acid [RNA]). They will be analyzed at a central laboratory for HAV, HBV, HCV, HIV-1/2, and parvovirus B19.

In case the result is positive, additional testing will be performed as necessary.

A pre-infusion serum sample for viral safety from each patient will be kept at ≤ -70°C at the central laboratory for possible future testing.

7.3.8 Vital Signs and Physical Examination

The vital signs obtained at the time points specified in Flowchart of Assessments Table 1 and Section 6 are blood pressure, body temperature, pulse rate, and respiratory rate. Vital signs will be closely monitored pre-injection, once during the injection, and within 30 minutes to 1 hour post-injection.

Physical examinations will be performed at the visits specified in Flowchart of Assessments Table 1 and Section 6. Both height and weight will be measured at screening.

7.3.9 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs up to 4 weeks after the IMP administration should be reported by the Investigator to the Sponsor in case the Investigator becomes aware of it. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring within 4 weeks after the last IMP administration should also be reported, regardless of whether they are considered treatment-related.

b) Pregnancies

Every effort will be made to avoid a pregnancy (including pregnancy in a female partner of a male patient) during the use of an IMP. A pregnancy test will be done for all women of childbearing potential to exclude pregnant patients.

Women of childbearing potential are defined as fertile women, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Pregnancies occurring in female patients and in female partners of male patients during the study (fetal exposure to the IMP) need to be reported by the Investigator using a Pregnancy Notification Form. The form must be submitted to the Sponsor or designee following the SAE reporting instructions provided in section 7.3.4. .

Follow-up information will be requested by a Sponsor representative for female patients on the outcome of both mother and fetus, for female partners of male patients on the outcome of the fetus.

Overdose, interaction, and medication error

The following safety relevant information should be reported as an AE or, if the reaction fulfills one of the criteria for seriousness, as an SAE.

c) Drug overdose

An overdose is a clinically relevant (causing symptoms and/or requires medical intervention), deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose. The reaction must be clearly identified as an overdose.

d) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

e) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labeling. The reaction must be clearly identified as a medication error.

7.4 Appropriateness of Measurements

Blood levels of C1-INH activity provide a direct measure of the amount of C1-INH in each patient. To ensure standardization and quality control of the PK measurements, the collected patient samples will be sent to a central laboratory for analysis. The planned safety assessments are standard assessments and are generally accepted for this kind of study.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participated in this study.

All data entered in the eCRF must be supported by source data in the patient records.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review, and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (e.g., sub-investigators, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Case Report Forms

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff (e.g., research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

8.1.3 Changes to Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and ‘manual’ queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed, and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An IB will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning the IMP becomes available.

The Investigator will be informed about the methods for rating relevant study outcomes and for completing eCRFs to reduce discrepancies between participating Investigator and study sites.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

A laboratory manual detailing the procedures for the central laboratory samples will be distributed to all study sites.

8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (e.g., sub-investigators, nurses) is authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all eCRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification list, which provides the unique link between named source records and eCRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patients' confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An IDMC will be established by the Sponsor. The IDMC will be composed of recognized experts in the field of allergy/immunology who are not actively recruiting patients.

The IDMC will review aggregated safety data after treatment of the first 6 patients enrolled in the study. Enrollment will be stopped after the 6th patient and only be allowed again after the IDMC recommendation to proceed. Pre-screening of new patients will be allowed while the IDMC decision is pending. The IDMC will then decide whether it is safe to continue dosing for the remaining patients. Thereafter, it will review relevant data quarterly during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific procedure will define in detail the composition, responsibilities, and procedures of the IDMC.

The IDMC will have access to the IB for OCTA-C1-INH, which includes any ADRs that have been observed with the IMP.

IDMC review determinations will be communicated to investigators by the Sponsor/the Sponsor's designee.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external contract research organization (CRO). All Sponsor procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

To account for possible early discontinuations or missing PK data, it is planned to enroll a total of 20 patients to have 18 evaluable patients, allowing for a drop-out rate of up to 10%.

The chosen number of at least 18 evaluable patients is not derived from statistical considerations of power, but to gather sufficient data for an accurate characterization of the PK properties of OCTA-C1-INH.

The mean baseline corrected AUC of C1 INH is expected to be in the magnitude of 2000 IU×hr/mL with a corresponding coefficient of variation of about 0.35. With these assumptions, the AUC analysis would result in a 90% confidence interval with a half width of about 286 IU×hr/mL.

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

9.2.1 Populations for Analysis

The following analysis sets will be considered for the statistical analysis:

Safety analysis set (SAF) consists of all patients who received the IMP injection.

Full analysis set (FAS) is defined according to the intention-to-treat (ITT) principle and consists of all patients of the safety analysis set who satisfy all eligibility criteria and for whom any post-baseline data is available; it is the set of eligible patients with treatment effects measured.

Per-protocol (PP) set consists of all patients of the FAS excluding those with protocol deviations which may have an impact on the analysis of the primary endpoint. This is the set of patients who participated in the study as intended and for whom the primary endpoint can be evaluated as planned.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP set. Examples of protocol deviations to be considered in this respect would be violations of the study entry criteria, dosing errors, or the use of prohibited concomitant medications.

The analysis of safety will be based on the safety set.

The evaluation of the primary objective will be performed on the FAS (ITT analysis) and the PP set (PP analysis).

The final decision regarding inclusion/exclusion of patients from the analysis sets will be made by a panel including the Clinical Project Manager, the study statistician and a medical expert during a data review meeting before database lock. The decisions will be based on a review of complete data listings and documented before the database is locked and the analysis is performed.

9.2.2 Pharmacokinetic Analysis Plan

9.2.2.1 Primary Endpoint

OCTA-C1-INH concentration-time data will be used to determine PK parameters by non-compartmental analysis methods using Phoenix® WinNonlin® (Certara) Version 6.3 (or higher). Actual sampling times relative to start of dosing rather than nominal times will be used in the calculation of all derived PK parameters. Pharmacokinetic concentration data will be listed by nominal time-point and will include the actual sampling times. Concentration data will be summarized by nominal time-point. Individual concentration-time plots will be presented in linear and semi-logarithmic displays. Mean concentration-time plots will be presented in linear and semi-logarithmic scale. PK parameters will be summarized in tabular form. Details of the PK non-compartmental analysis and the PK concentration and parameter tables, listings, and figures will be specified in the Statistical Analysis Plan (SAP).

9.2.2.2 Secondary Endpoints

The secondary PK analyses will comprise of PK parameters derived from the individual concentration time data of levels of C1-INH antigen, and C4 level, using the same methods described for primary PK analysis.

9.2.3 Safety Analysis Plan

The safety analysis will comprise descriptive statistics, tabulations, and listings of all TEAEs, laboratory results, viral nuclear antigens, vital signs, presence of anti-C1-INH antibodies, and physical examination findings.

All reported AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 22.0). The absolute and relative frequencies of patients with at least 1 TEAE will be determined. Furthermore, the absolute and relative frequencies of each individual TEAE preferred term will be presented. Summary tables for TEAEs will be given by system organ class and preferred term. Additionally, AEs will be summarized by severity, relationship to study treatment, and actions taken.

To assess possible temporal relationships between IMP administration and the occurrence of AEs, the number of patients experiencing an AE within 24 hours of injection and the number of injections associated with AEs occurring within 24 hours of injection will be reported in total, by system organ class and by preferred term.

Narratives will be prepared by a medical expert describing each death, each SAE, and those of the other significant AEs that are judged to be of special interest because of clinical importance (AESIs). The narrative will address the following: nature and severity of event, clinical course leading up to event, with an indication of timing relevant to IMP administration, relevant laboratory measurements, whether the drug was stopped, actions taken or post-mortem findings (if any), and a causality assessment.

Statistical analysis of vital signs and laboratory parameters will consist of descriptive tables on sampling statistics for the values as well as their changes from before to after injection.

Physical examination findings at baseline and any changes in the physical examination findings at the termination visit will be listed.

9.2.4 Handling of Missing Data

In general, missing data will not be imputed, and the PK analysis will be based on actual measures and exact sampling time points only. Any PK profile with missing values will be evaluated individually to assess if and how it can be used for PK parameter estimations, to ensure the validity of the PK analysis. Any decision in this respect will be made and documented prior to database lock.

9.3 Enrollment

A listing of all enrolled patients will be provided. Screening failures and reasons for failure will also be listed.

9.4 Interim Analysis

No interim analysis is planned.

10 ETHICAL/REGULATORY, LEGAL, AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (e.g., CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name, date, and time noted by the patient, before the patient is exposed to any study-related procedure, including pre-screening tests for eligibility. Pre-screened subjects have to re-consent at screening.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the eCRF for each patient enrolled.

Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Co-ordinating Investigator and the Sponsor prior to its implementation. Any such amendments will be submitted to the

any competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patients' confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential patient identification list, original consent forms, and source records will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness, and accuracy of all eCRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's standard operating procedures) will be prepared by the Sponsor after completion of the study. The Co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multicenter studies only in their entirety and not as individual site data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for administering the IMP according to this protocol and for its secure storage and safe handling throughout the study.

14 APPENDICES

Not applicable.

15 REFERENCES

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