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Pharmacokinetics and safety of IV Injection of OCTA-C1-INH in hereditary angioedema

Submission date
06/12/2019

Recruitment status
No longer recruiting

Registration date
17/03/2020

Overall study status
Completed

Last Edited
16/06/2022

Condition category
Other

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The study drug OCTA-C1-INH is a product containing C1 esterase inhibitor (C1-INH). C1-INH is a protein naturally extracted from human blood plasma. The disorder “hereditary angioedema” (abbreviation HAE) is an inherited condition which leads to either unsatisfactory amounts of C1-INH or non-functioning C1-INH protein. Normally C1-INH helps to regulate the blood-based systems involved in disease-fighting in the immune system and for blood clotting. If defective the C1-INH does not perform its regulatory function well and an imbalance occurs in the blood-based systems. Therefore substances are produced that lead to a release of fluids into surrounding tissue resulting in edema (swelling) in different parts of the body. Several different types of HAE have been described. HAE type I is the most common form and is caused by decreased production of C1-INH. In HAE type II the amount of C1-INH in the blood is not decreased but its functionality is impaired. The therapeutic effect of C1-INH products in HAE types I and II is induced by replacement of the lacking C1-INH activity. C1-INH replacement therapy with human plasma-derived C1-INH concentrate is an effective and well-tolerated treatment for HAE. OCTA-C1-INH is a stable, sterile, virus-inactivated and highly purified concentrate of C1-INH derived from human plasma. It is available as a freeze-dried powder for intravenous administration as injection. OCTA-C1-INH will be developed for therapy of acute HAE attacks at a dose of 20 international units (IU per kilogram body weight) in patients with inborn C1-INH deficiency aged 18 years or older. OCTA-C1-INH has not been administered to any human being yet. Further clinical studies are needed until its potential use as a therapy of acute HAE attacks. The reason for this first clinical study is to investigate the pharmacokinetic (PK) properties and safety of OCTA-C1-INH. The term pharmacokinetic means that the movement of the study drug within the body will be investigated, in particular the rates of the movements are of interest.

Who can participate?
Patients aged 18 and over with (among others) documented congenital C1-INH deficiency with C1 INH functional activity less than 50% and C4 level below the laboratory reference range and without 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.

What does the study involve?
The study involves taking several blood samples over a period of time to find out how the body handles the study drug. The entire study period will be a maximum of 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. An optional Pre-Screening visit with PK sampling for confirmation of the HAE type I or type II diagnosis and then 13 PK sample timepoints are planned. Additionally, pregnancy tests, weight measurement, physical examinations, safety lab tests at 4 timepoints and at 2 timepoints viral nuclear antigen testing and a one time IMP intravenous injection will be performed as well as Wells probability scores for DVT and PE at 3 timepoints with Doppler screening for DVT and a blood sample for D-dimers in case of Well's DVT probability score result being ≥ 2. Mandatory hospitalization for patient observation during and after administration of OCTA-C1-INH is required for at least 24 hours.

What are the possible benefits and risks of participating?
The study will provide critical information about OCTA-C1-INH useful for the design and conduct of following clinical trials. Introducing OCTA C1-INH to the market will help in meeting the needs of HAE patients. Study drug potential side effects known from other C1-INH medications (working like the study drug) available on the market and typical for this kind of medical products are as follows: hypersensitivity reactions, anaphylactic reactions, in very rare cases thromboembolic events, transmission of infectious agents, and there may be previously unrecognized risks that might occur (including risks to an embryo or fetus in case of pregnancy) beside the discomforts caused by injection of study drug and blood sampling. Participants in this study will be under careful medical observation. A number of tests will be conducted to ensure safety. There is no guarantee that participants will have any direct medical benefits by taking part in this study.

Where is the study run from?
The study is performed in Ukraine, Russia, Belarus, and Germany at about 10 sites

When is the study starting and how long is it expected to run for?
August 2019 to February 2021

Who is funding the study?
Octapharma Pharmazeutika Produktionsges.m.b.H. (Austria)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-001693-28

Protocol serial number
CONE-01-V05_Final_30-Dec-2020 (all countries except UKR) and CONE-01-V05.1_Final_30-Dec-2020 (UKR only)

Study information

Scientific Title
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

Acronym
CONE-01

Study objectives
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.

Ethics approval required
Old ethics approval format

Ethics approval(s)

1. Germany:
1.1. Approved 28/11/2019, Ethics committee at state Chamber of Physicians in Hessen (Ethik-Kommission bei der Landesärztekammer Hessen, Hanauer Landstrasse 152, 60314 Frankfurt am Main, Germany; +49 (0)69 97672-317; ethikkommission@laekh.de), ref: # 2019-1378-fAM
1.2. Approved 06/02/2020, Paul Ehrlich Institute (Paul-Ehrlich-Str. 51-59, 63225 Langen, Germany; +49 (0)6103 771811; ct@pei.de)
2. Ukraine:
2.1. Approved 20/01/2020, Ukrainian Ministry of Health (7 Hrushevskoho Street, Kyiv, Ukraine, 01601; +380 (0)44 226 22 05; moz@moz.gov.ua)
2.2. Approved 20/01/2020, committee on bioethics and deontology of SI Institute of Otolaryngology n.a. Prof. O.S. Kolomiychenko of NAMS of Ukraine (3, Zoolohichna street, Kyiv 03057, Ukraine; +38 (0)44 483 29 90; uapras@ukr.net)
2.3. Approved 22/01/2020, Ethics Committee of Municipal Non-Commercial Enterprise of Lviv Regional Council "Lviv Regional Clinical Hospital" (7, Chernihivska str, Lviv city, 79010 Ukraine; +38 (0)32 275 76 31; lokl_lec@ukr.net)
3. Russia:
3.1. Approved 01/06/2020, Ministry of Health of the Russian Federation (3, Rakhmanovskiy per., GSP-4 Moscow 127994; +8 (0)495 628 44 53, +8 (0)627 29 44)
3.2. Approved 26/08/2020, Local Ethics Committee of National Research Center Institute of Immunology of Federal Medical and Biological Agency of Russia (24, Kashirskoye shosse, Moscow 115478 Russia; +7 (0)499 6128135; email: not applicable)
3.3. Approved 27/08/2020, Saint Petersburg Scientific Research Institute of Epidemiology and Microbiology Named After Pasteur (Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, 14 Mira Str., Saint Petersburg, 197101, Russia; +7 (0)812 233 34 20; email: not applicable)
3.4. Approved 15/09/2020, Committee on Ethics of Scientific Research at Federal State Budget Educational Institution of Additional Professional Education "Russian Medical Academy of Continuous Postgraduate Education" of Ministry of Healthcare of Russia (2/1, Barrikadnaya st., bldg.3, Moscow, 125993, Russia; +7 (0)495 680 05 99 (ext. 1591); email: not applicable)
4. Belarus:
4.1. Approved 25/03/2020, Ministry of Health of the Republic of Belarus (220048, Minsk, 39 Myasnikova St; mzrb@belcmt.by), approved protocol 5.0 10/03/2021
4.2. Approved 24/08/2020, Ethics Committee of Grodno University Clinic (52, Leninsky Komsomol Blvd, 230017, Grodno, Belarus; +375 (0)80152436230; email: not applicable)
4.3. Approved 07/09/2020, Ethics Committee of Republican Research and Applied Centre for Medical Radiology and Human Ecology (290, Ilyicha str., 246040, Gomel, Belarus;+375 (0)232 378095; email: not applicable), approved protocol 5.0 19/02/2021

Study design
Prospective open-label single-arm multicenter phase 2a study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Hereditary angioedema (HAE) type I or type II

Interventions

Current interventions as of 30/09/2020:

The IMP used in the study OCTA-C1-INH is a lyophilized powder for solution for injection together with a solvent (water for injection [WFI]). The IMP will be administered as a single dose of 20 IU/kg body weight as a slow intravenous injection. The IMP has a potency of 200 IU/mL C1-INH.

The following PK parameters will be measured: OCTA C1 INH blood concentrations at each sampling time, Cmax, Tmax, CL, AUC, AUCnorm, MRT, IR, Vd, and T1/2.

The safety parameters are:
1. Number and severity of adverse events (AEs)
2. Change in vital signs from pre- to post-injection
3. Change in laboratory parameters from pre- to post-injection
4. 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
5. Anti-C1-INH antibodies

The study has scheduled an optional Pre-Screening visit and then Visit 1 to Visit 9 on day Screening, day zero, day 1 to 3 and day 5 to 7 with the final Visit (9) on day 14 (which would be also the early discontinuation visit).

PK samples will be taken on the optional pre-Screening Visit and then as a single pre-IMP-injection sample, at 6 time points after IMP-injection (timepoints 0 minutes, 15 minutes, 1 hour, 2 hours, 6 hours, 12 hours) on day zero and then on consecutive visits on day 1 to 3 and day 5 to 7 (24 hours, 48 hours, 72 hours and 120 hours, 144 hours, 168 hours).
Viral nuclear antigen testing will be done at Screening Visit and at last Visit #9 or at the discontinuation Visit.

Anti-C1-INH antibodies will be tested at timepoint pre-IMP-injection and last Visit #9 or discontinuation Visit.

Routine safety laboratory tests will be done at Screening Visit, pre-IMP-injection, at Visit day 1 and at last Visit #9 or discontinuation Visit.

Vital signs will be checked at Screening visit, timepoint pre-IMP-injection, during IMP injection and post-IMP injection as well as at last Visit #9 or discontinuation Visit.

Physical examination will be checked at Screening visit, timepoint post-IMP-injection and at last Visit #9 or discontinuation Visit.

IMP injection intravenous on day 2. Mandatory hospitalization for patient observation during and after administration of OCTA-C1-INH is required for 24 hours. Hospitalization beyond the 24 hours period is recommended and can be done according to local clinical practice.

Body weight measurement at Screening visit.

Pregnancy tests will be performed at Screening visit, timepoint pre-IMP-injection and at last Visit #9 or discontinuation Visit.

Previous interventions:

The IMP used in the study OCTA-C1-INH is a lyophilized powder for solution for injection together with a solvent (water for injection [WFI]). The IMP will be administered as a single dose of 20 IU/kg body weight as a slow intravenous injection. The IMP has a potency of 200 IU/mL C1-INH.

The following PK parameters will be measured: OCTA C1 INH blood concentrations at each sampling time, Cmax, Tmax, CL, AUC, AUCnorm, MRT, IR, Vd, and T1/2.

The safety parameters are:
1. Number and severity of adverse events (AEs)
2. Change in vital signs from pre- to post-injection
3. Change in laboratory parameters from pre- to post-injection
4. 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
5. Anti-C1-INH antibodies

The study has scheduled an optional Pre-Screening visit and then Visit 1 to Visit 9 on day Screening, day zero, day 1 to 3 and day 5 to 7 with the final Visit (9) on day 14 (which would be also the early discontinuation visit).

PK samples will be taken on the optional pre-Screening Visit and then as a single pre-IMP-injection sample, at 5 time points after IMP-injection (timepoints 0 minutes, 15 minutes, 1 hour, 6 hours, 12 hours) on day zero and then on consecutive visits on day 1 to 3 and day 5 to 7 (24 hours, 48 hours, 72 hours and 120 hours, 144 hours, 168 hours).

Viral nuclear antigen testing will be done at Screening Visit and at last Visit #9 or at the discontinuation Visit.

Anti-C1-INH antibodies will be tested at timepoint pre-IMP-injection and last Visit #9 or discontinuation Visit.

Routine safety laboratory tests will be done at Screening Visit, pre-IMP-injection, at Visit day 1 and at last Visit #9 or discontinuation Visit.

Vital signs will be checked at Screening visit, timepoint pre-IMP-injection, during IMP injection and post-IMP injection as well as at last Visit #9 or discontinuation Visit.

Physical examination will be checked at Screening visit, timepoint post-IMP-injection and at last Visit #9 or discontinuation Visit.
IMP injection intravenous on day 2.

Body weight measurement at Screening visit.

Pregnancy tests will be performed at Screening visit, timepoint pre-IMP-injection and at last Visit #9 or discontinuation Visit.

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
OCTA-C1-INH

Primary outcome(s)
The PK parameters of OCTA-C1-INH, measured as C1-INH activity at the optional pre-screening, day 0 pre-injection and six timepoints post-injection (0, 15 minutes, 1, 2, 6, and 12 hours), day 1, 2, 3, 5, 6, and day 7. The PK parameters that will be assessed for OCTA-C1-INH include:
1. Blood concentrations at each sampling time
2. Maximum blood concentration (Cmax)
3. Time to maximum concentration (Tmax)
4. Clearance (CL)
5. Area under the concentration-time curve (AUC)
6. AUC normalized by the dose (AUCnorm)
7. Mean residence time (MRT)
8. Incremental recovery (IR)
9. Volume of distribution (Vd)
10. Elimination half-life (T1/2)

Key secondary outcome(s))
1. PK parameters of the following analytes after a single IV administration of OCTA-C1-INH:
1.1. C1-INH antigen measured at day 0 pre-injection and 6 time points post-injection (0, 15 minutes, 1, 2, 6, and 12 hours), day 1, 2, 3, 5, 6, and day 7
1.2. C4 level measured at the optional pre-screening, day 0 pre-injection and 6 time points post-injection (0, 15 minutes, 1, 2, 6, and 12 hours), day 1, 2, 3, 5, 6, and day 7
All PK parameters determined for the primary PK endpoint will also be determined for the secondary PK endpoints
2. Safety parameters:
2.1. Number and severity of adverse events (AEs) documented starting at day 0 and throughout the study
2.2. Number and severity of adverse events of special interest (AESIs) of thromboembolic event (TEE) type
2.3. Change in vital signs from pre- to post-injection measured at screening, day 0 (pre/during /post-injection), and day 14
2.4. Change in laboratory parameters from pre- to post-injection measured at screening, day 0 pre-injection, (day 1 in the first 6 patients only), and day 14
2.5. 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 measured at screening and day 14
2.6. Anti C1-INH antibodies measured at day 0 pre-injection and day 14.

A Well's PE and DVT probability score will be performed at three timepoints; in case the Well's DVT probability score result is ≥ 2 then a Doppler screening for DVT will have to be completed (recommended: Doppler using color duplex sonography) and a blood sample taken for D-dimers.

Completion date
17/02/2021

Eligibility

Key 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
6. Fertile male patients must agree to use acceptable methods of contraception from screening until final visit

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
20

Key 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
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). Updated 09/03/2021: Any 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/m2 and experiencing obesity-related health conditions or ≥40 to 44.9 kg/m2), 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

Date of first enrolment
15/09/2020

Date of final enrolment
03/02/2021

Locations

Countries of recruitment
Belarus

Germany

Russian Federation

Ukraine

Study participating centre
Hämophilie-Zentrum Rhein Main GmbH
Hessenring 13a
Mörfelden-Walldorf
Germany
64546

Study participating centre
Grodno University Clinic
Department of Allergology
52, Leninsky Komsomol Blvd
Grodno
Belarus
230017

Study participating centre
Republican Research and Applied Center for Medical Radiology and Human Ecology
290, Ilyicha str.
Gomel
Belarus
246040

Study participating centre
Russian Medical Academy of Continuous Postgraduate Education
Ministry of Health of the Russian Federation
Clinical Allergology Department
2/1, Barrikadnaya str., bldg 1
Moscow
Russian Federation
123955

Study participating centre
National Research Center Institute of Immunology
Federal Medical and Biological Agency
Adult Immunopathology Department
24, Kashirskoye shosse
Moscow
Russian Federation
115478

Study participating centre
Saint Petersburg Scientific Research Institute of Epidemiology and Microbiology named after Pasteur
Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing
14, Mira str.
St. Petersburg
Russian Federation
197101

Study participating centre
O.S. Kolomiychenko Institute of Otolaryngology of National Academy of Medical Sciences of Ukraine
Center of allergic diseases
3, Zoolohichna str.

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03057

Study participating centre
Lviv Regional Clinical Hospital
Rheumatology department
7, Nekrasova str.
Lviv
Ukraine
79010

Sponsor information

Organisation
Octapharma (Austria)

ROR
https://ror.org/022k50n33

Funder(s)

Funder type
Industry

Funder Name
Octapharma Pharmazeutika Produktionsges.m.b.H

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available as this is an industry-sponsored clinical trial. Upon completion of the clinical study report data will be held at Octapharma Pharmazeutika Produktionsges.m.b.H. Department CR&D and results are planned to be published in a peer-reviewed journal.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		17/02/2022	16/06/2022	No	No
Protocol file	version V2.2	30/01/2020	09/04/2020	No	No
Protocol file	version V4	29/04/2020	17/08/2020	No	No
Protocol file	version 5.0	30/12/2020	16/12/2021	No	No
Protocol file	version 5.1	30/12/2020	16/12/2021	No	No