Plasma-derived C1 esterase inhibitor pharmacokinetics and safety in patients with hereditary angioedema

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Background: Over 40 years of use demonstrates that complement 1 esterase inhibitor (C1-INH) concentrate is effective and well tolerated for acute edema attacks and prophylaxis in patients with hereditary angioedema. OCTA-C1-INH is a new stable, virus-inactivated, nanofiltrated concentrate of C1-INH derived from human plasma.

Objective: We investigated the pharmacokinetics and safety profile of new C1-INH in people with hereditary angioedema during an attack-free period.

Methods: In this prospective, multicenter, open-label, single-arm study, adults with hereditary angioedema type I/II received a single intravenous dose of 20 IU/kg C1-INH. Blood samples were taken ≤30 minutes before infusion, and 0, 0.25, 1, 2, 6, 12, 24, 48, 72, 120, 144, and 168 hours after infusion. The primary end point was assessing the pharmacokinetic parameters of C1-INH measured by C1-INH activity. Safety end points were also examined.

Results: Twenty patients received a single dose of 20 IU/kg new C1-INH with a mean (standard deviation) total dose of 1457.3 (356.51) IU. Mean (standard deviation) area under the curve normalized by dose was 51.6 (17.9) h•IU/mL/IU, maximum blood concentration was 1.14 (0.989) IU/mL, incremental recovery was 0.0466 (0.051) (IU•kg)/(IU•mL), half-life was 0.598 (0.716) hours, and time to maximum concentration was 0.598 (0.716) hours. No thromboembolic events were recorded. No treatment-emergent adverse events were rated as severe/serious.

Conclusion: PK parameters of new C1-INH were in line with those reported for other C1-INH concentrates. New C1-INH demonstrated a favorable safety profile in patients with C1-INH deficiency. Further studies are warranted to determine the effectiveness and longer-term safety of new C1-INH. (J Allergy Clin Immunol Global 2024;3:100178.)

Key words: *Complement 1 esterase inhibitor, hereditary angioedema, open-label, pharmacokinetic, plasma-derived, safety*

Hereditary angioedema (HAE) is a rare disorder characterized by attacks of edema, which affect various parts of the body. Subcutaneous edema typically affects the face, hands, arms, legs, or genitals, while swelling of abdominal organs can cause diarrhea, vomiting, and severe pain.[1] Laryngeal edema, if not treated, can ultimately lead to death by asphyxiation.[2,3]

Various types of HAE have been described. HAE type I is the most common and is caused by deficient synthesis of the complement 1 esterase inhibitor (C1-INH) protein. HAE type II is characterized by normal plasma levels but impaired functionality of the C1-INH molecule. Since 2000, further types of HAE were described, characterized by normal C1-INH levels and function. HAE with normal C1-INH is associated with several different mutations in genes involved in kallikrein–kinin system activation, although the mechanism of pathology is uncertain.[4,5] All types of HAE are characterized by the similar symptoms.[2,6] HAE types I and II are present in childhood in around 50% of cases.[7]

Here, we focus on HAE due to C1-INH functional deficiency (HAE types I and II). Clinical management of HAE consists of treatment of HAE attacks to reduce the severity and duration of the symptoms, and short- or long-term prophylaxis if attacks are frequent. For treatment of acute attacks, bradykinin antagonists (icatibant), kallikrein inhibitors (ecallantide), plasma-derived or recombinant C1-INHs, or fresh frozen plasma are used.[6,8] For long-term prophylaxis, kallikrein inhibitors, bradykinin receptor antagonists, and plasma-derived C1-INH (pdC1-INH) are used. Other medications include synthetic attenuated androgens and antifibrinolytic agents (tranexamic acid). These treatment options are not available in all countries and areas, and adverse effects may occur. Although the safety and tolerability of icatibant are good, transient injection-site reactions can occur.[6] Ecallantide is associated with potentially serious hypersensitivity reactions, including anaphylaxis.[6] Attenuated androgens may be associated with a number of adverse effects, including masculinization and

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Abbreviations used

AE: Adverse event
AUC_{inf}: Area under concentration–time curve to infinity
AUC_{norm}: Area under concentration–time curve normalized by dose
C1-INH: Complement 1 esterase inhibitor
COVID-19: Coronavirus disease 2019
FAS: Full analysis set
HAE: Hereditary angioedema
IDMC: Independent data monitoring committee
LDH: Lactate dehydrogenase
pdC1-INH: Plasma-derived C1-INH
PK: Pharmacokinetic
SD: Standard deviation
TEAE: Treatment-emergent AE
TEE: Thromboembolic event

growth retardation in children when used for long-term prophylaxis, so antifibrinolytics are preferred because of their better safety profile; however, the efficacy of antifibrinolytics has been questioned and is not adequately supported by the data.[6]

Prospective studies[9-13] and over 40 years of use in the clinic[14] demonstrate that C1-INH concentrate is effective and well tolerated as both treatment for acute edema attacks and prophylaxis in patients with HAE.[13] The 2021 guidelines from the World Allergy Organization/European Academy of Allergy and Clinical Immunology[15] recommended pdC1-INH as first-line treatment for both long- and short-term prophylaxis, and also as first-line therapy for acute HAE attacks. Currently, 3 intravenously administered C1-INH products are available in Europe and North America: plasma-derived Berinert (CSL Behring)[16] and Cinryze (Takeda),[17] as well as a recombinant C1-INH product, Ruconest (Pharming),[18] with approved product indications varying in different countries.[15] The plasma-derived C1-INH HAEgarda (CSL Behring)[19] and Berinert[20] are administered subcutaneously and are licensed for use in North America and Europe, respectively.

OCTA-C1-INH is a new stable, sterile, virus-inactivated, nanofiltrated, highly purified concentrate of C1-INH derived from human plasma. Objectives of this study were to investigate the pharmacokinetic (PK) characteristics and safety profile of the new C1-INH in people with HAE during an attack-free period. Results showing that the new C1-INH is effective and well tolerated would support its licensing for use, providing another therapeutic option for patients with HAE.

METHODS

Study design

This was a prospective, open-label, single-arm, multicenter study in 20 adults with HAE type I or II. The study was conducted at 6 centers in Belarus, the Russian Federation, and Ukraine and all investigators were selected because they were physicians treating HAE patients. The study was a Phase 2a study in Belarus and the Russian Federation and a Phase 1 study in Ukraine (as requested by the health ministry of Ukraine). The study was conducted from September 2020 to February 2021, during the coronavirus disease 2019 (COVID-19) pandemic. The COVID-19 pandemic did not affect the conduct of the study.

The study was approved by central or local ethics committees. Freely given written consent was obtained from all patients before entering the study. The study was conducted according to good clinical practice, applicable regulatory requirements, national law, and the ethical principles of the Declaration of Helsinki. The study was registered at the ISRCTN Registry (www.isrctn.com) as ISRCTN36746902.

Patients

Male and female patients aged ≥18 years at the informed consent date with documented congenital C1-INH deficiency —that is, C1-INH functional activity <50% and C4 level below the laboratory reference range—were eligible for the study. Women of childbearing potential were required to provide a negative pregnancy test at screening and before infusion, and both women of childbearing potential and fertile men were required to use acceptable methods of contraception from screening until the final visit.

Key exclusion criteria were that patients were not permitted to enter the study if they displayed any signs of an HAE attack, had experienced an HAE attack within 7 days before dosing with the new C1-INH, or had more than 9 HAE attacks in total over the 3 months before dosing with the new C1-INH. Treatment with C1-INH, nonbiological bradykinin pathway inhibitors (eg, ecallantide, icatibant), or tranexamic acid within 2 weeks before dosing with the new C1-INH was not permitted; nor was treatment with lanadelumab within 11 weeks before the new C1-INH dosing. Female patients receiving estrogen-containing contraceptives, hormone replacement therapy (excluding progesterone-only contraceptives, which were permitted), or selective estrogen receptor modulators (eg, tamoxifen) were also not eligible for inclusion; nor were patients receiving androgen therapy (eg, testosterone, danazol, dehydroepiandrosterone/androstenedione). Finally, patients were not eligible for inclusion who exhibited risk factors for thromboembolic events (TEE), including the presence of an indwelling venous catheter or access device, history of thrombosis, underlying atherosclerosis, morbid obesity (body mass index ≥ 35 kg/m^2 and experiencing obesity-related health conditions, or body mass index ≥ 40 to 44.9 kg/m^2), immobility, or medications known to increase thromboembolic risk.

Study procedures

Eligible patients were enrolled and, within 14 days after screening, received a single dose of 20 IU/kg body weight of the new C1-INH administered by slow intravenous injection (Fig 1). Patients were required to remain at the study site for observation during and for at least 24 hours after administration of C1-INH, according to local clinical practice. In the event that a patient experienced an HAE attack during the study before PK sampling was completed, standard-of-care treatment was applied, and the patient was discontinued from the study.

End points, sampling, and analyses

The primary end point was the PK parameters of the new C1-INH, measured as C1-INH activity, including area under the concentration–time curve (AUC); AUC normalized by dose

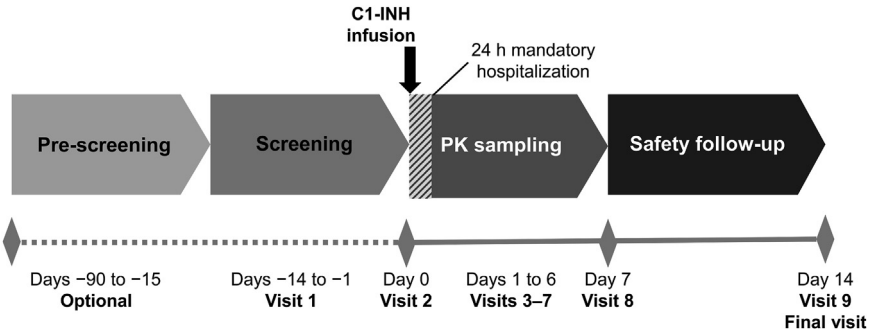

FIG 1. Study flow.

(AUC_{norm}); clearance; maximum blood concentration; incremental recovery; mean residence time; half-life; time to maximum concentration; and volume of distribution. Secondary end points included the above PK parameters as measured by C1-INH antigen and C4 level. Blood samples for PK analysis were taken at ≤30 minutes before infusion, 0 minutes, and at 15 minutes and 1, 2, 6, 12, 24, 48, 72, 120, 144, and 168 hours after infusion, to test for C1-INH activity, C1-INH antigen concentration, and C4 level. Testing was performed at the central laboratory.

Safety

Safety end points included the number and severity of adverse events (AEs); the number and severity of AEs of special interest of TEE type; changes in vital signs or laboratory parameters from before to after infusion; and the presence of anti–C1-INH antibodies.

AEs were collected throughout the study, from before infusion to day 14 after infusion, and follow-up via telephone was performed at 4 weeks after infusion. AEs were coded using the Medical Dictionary for Regulatory Activities, version 23.0. For each AE, the severity (mild, moderate, or severe), seriousness (nonserious or serious), and causality (probable, possible, unlikely, or unrelated) were assessed by the investigator. Any AE recorded after the start of study drug administration was considered to be treatment emergent and was documented as a treatment-emergent AE (TEAE). The Wells scoring criteria for the assessment of possible or probable deep-vein thrombosis and for pulmonary embolism, which were modified according to the National Institute for Health and Care Excellence (aka NICE) Clinical Guideline 144 (2012),[21] were performed at days 1, 5, and 14 after infusion (see Table E1 in this article's Online Repository at www.jaci-global.org).

Vital signs were measured at screening; on day 0 before, during, and after administration of C1-INH; and at the final visit on day 14 after infusion.

Blood samples were taken for routine safety laboratory tests, including hematology and clinical chemistry, at screening, the day of infusion, day 1 for the first 6 patients, and day 14 after infusion (final visit) for all patients. Blood samples for testing for anti–C1-INH antibodies were taken before infusion and on day 14 after infusion. These samples were analyzed at the central laboratory.

Samples for serology and blood nuclear antigen testing were collected at baseline and at the final visit for all patients and were tested for hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus 1/2, and parvovirus B19.

Monitoring

An independent data monitoring committee (IDMC) reviewed the aggregated safety data after treatment of the first 6 patients enrolled onto the study. Enrollment was paused after the sixth patient completed the final study visit and resumed after the IDMC gave its recommendation to proceed.

Statistical methods

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

The safety analysis was performed in the safety population, consisting of all patients who received the new C1-INH infusion. Analysis of the primary PK end point was performed in the full analysis set (FAS), which was defined according to the intention-to-treat principle and consisted of all patients who received the new C1-INH, who satisfied all eligibility criteria, and for whom any data after baseline were available. Analyses were also performed in the per-protocol analysis set, which consisted of all patients in the FAS except those with protocol deviations that may have affected analysis of the primary end point.

All collected PK and safety parameters were listed and presented as descriptive statistics. All concentration values below the lower limit of quantification were set to zero. Results for C1-INH activity PK parameters were excluded if either the percentage of extrapolated AUC exceeded 20% of AUC to infinity (AUC_{inf}) or the coefficient of regression was <0.70.

RESULTS

Patient characteristics

A total of 23 patients were screened. Of these, 3 patients were ineligible because they did not have documented congenital C1-INH deficiency with C1-INH functional activity <50% and C4 level below the laboratory reference range. A total of 20 patients were enrolled in the study, received a single dose of the new C1-INH, and were included in the FAS.

TABLE I. Demographics of FAS of 20 patients

Characteristic	Value	
	Mean (SD)	Median (range)
Age (years)	36.7 (13.25)	38.5 (18-66)
Height (cm)	169.8 (9.00)	170.5 (156-185)
Weight (kg)	72.9 (17.83)	70.5 (45-109)
Body mass index (kg/m^2)	25.0 (4.65)	24.3 (17-34)
	No. (%)	
Sex		
Female	11 (55.0)	
Male	9 (45.0)	
Race		
White	20 (100)	

TABLE II. History of HAE at study entry for FAS of 20 patients

Characteristic	Value	
	Mean (SD)	Median (range)
C1-INH activity (IU/mL)*	0.0841 (0.168)	0 (0-0.51)
C1-INH antigen (g/L)*	0.1 (0.107)	0.05 (0.03-0.11)
HAE attacks in 6 months before study entry	6.5 (4.70)	6 (1-15)
	No.	
Location of swelling in last attack†		
Upper extremities	10	
Gastrointestinal tract	6	
Face	4	
Lower back	1	
Urticaria	1	
Treatment of last attack		
Icatibant	3	
Aminocaproic acid	2	
C1-INH	2	
Ketorolac	1	
None	12	
Concomitant medications		
Icatibant	2	
Danazol	1	
Desogestrel	1	
Bilastine	1	
Ibuprofen	1	
Bisoprolol	1	
Lercanidipine	1	
Indapamide	1	
Mometasone furoate	1	

*Values below lower limit of quantification were set to zero.
†Attacks affecting >1 location were reported for 2 patients.

A total of 29 major protocol deviations were recorded in 14 (70%) of 20 enrolled patients. Three of these protocol deviations involved a presumptive mix-up of the preinfusion and 0 minutes postdose PK samples, which we inferred on the basis of the implausible C1-INH levels we obtained, which resulted in data from 3 patients being excluded from the per-protocol analysis set.

For the FAS, the median age was 38.5 years (range, 18-66), 55% of patients were female (11/20), and 100% of patients were White (Table I).

Mean (standard deviation [SD]) C1-INH activity at baseline was 0.0841 (0.168) and mean C1-INH antigen levels were 0.1 (0.107) (Table II). All patients had experienced at least 1 HAE attack within the last 6 months (median, 6; range 1-15), which affected the upper extremities (n = 10), gastrointestinal tract (n = 6), face (n = 4), and lower back (n = 1; some patients experienced attacks affecting >1 location). One patient also experienced urticaria alongside swelling of the gastrointestinal tract. These attacks were treated with icatibant (n = 3), aminocaproic acid (n = 2), C1-INH concentrate (n = 2), or ketorolac (n = 1), with 12 attacks remaining untreated. Other concomitant medications that patients received are described in Table II.

Dosing

All 20 patients enrolled in the study received a single dose of 20 IU/kg of the new C1-INH as planned. The mean (SD) total dose

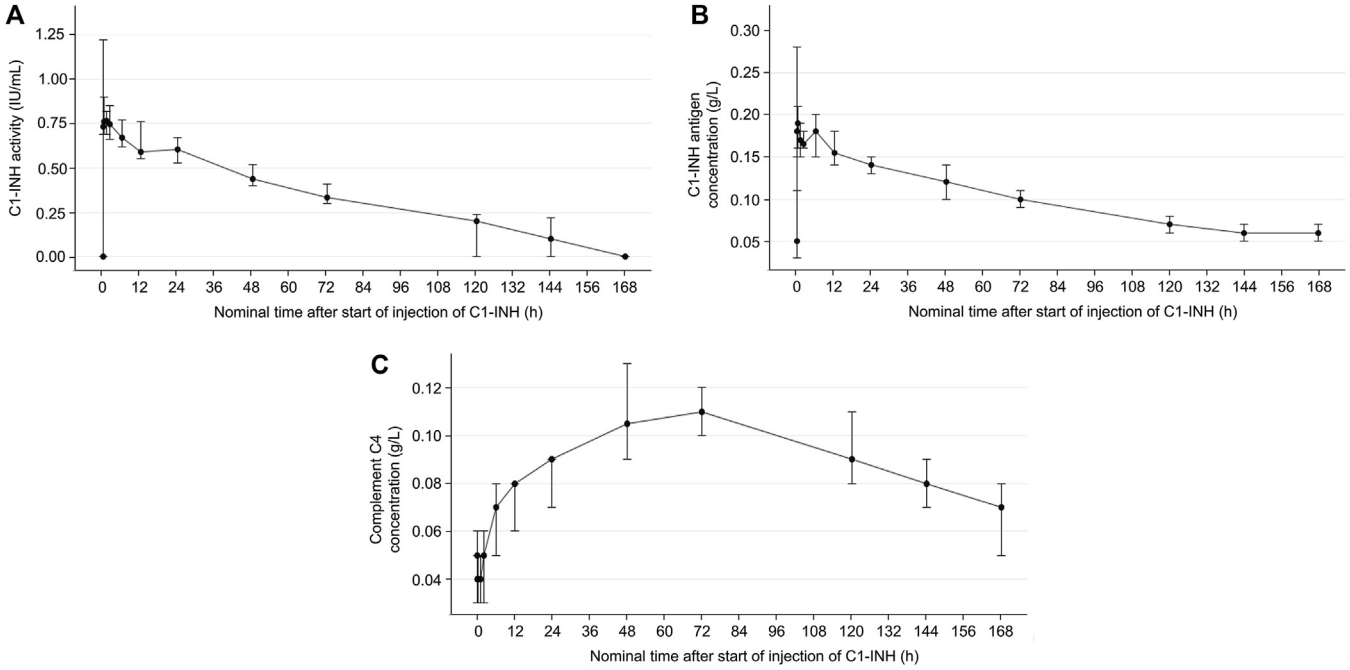

FIG 2. Median concentration–time profile of **(A)** C1-INH activity, **(B)** C1-INH antigen, and **(C)** C4 antigen after single intravenous dose of new C1-INH (FAS, N = 20). Error bars represent 95% distribution-free confidence intervals. Preinjection time was set to −5 minutes; all results below lower limit of quantification were set to 0 IU/L. Samples at preinfusion and 0 minutes postdose time points that constituted major protocol deviations were excluded from analyses; for these time points, n = 17. *IMP,* Investigational medicinal product.

TABLE III. C1-INH activity PK parameters for FAS of 20 patients

Parameter	No.	Mean (SD)	Median (range)	Geometric mean	Geometric mean CV (%)*
AUC_{last} (h•IU/mL/IU)	20	51.6 (17.9)	49.7 (25.6-83.9)	48.6	36.7
C_{max} (IU/mL)	20	1.14 (0.989)	0.85 (0.58-5.2)	0.973	49.8
C_{max}/D (IU/mL/IU)	20	0.00083 (0.000841)	0.000664 (0.000353-0.00433)	0.000687	54.7
IR ([IU•kg]/[IU•mL])	20	0.0466 (0.051)	0.0388 (–0.0065-0.246)	0.0367	91.4
$t_{½}$ (hours)	20	74.1 (19)	77.2 (39.5-109)	71.6	28.1
T_{max} (hours)	20	0.598 (0.716)	0.308 (0.0667-2.08)	0.295	189

AUC_{last}, AUC from time of dosing to time of last measurable concentration; *C_{max},* maximum blood concentration; *C_{max}/D,* C_{max} per dose; *CV,* coefficient of variation; *IR,* incremental recovery; *no.,* number of patients; *$t_{½}$,* half-life; *T_{max},* time to maximum concentration.
*Geometric CV (%) was calculated as [exp(SD2)−1]1/2×100, where SD was the standard deviation of the natural log-transformed data.

was 1457.3 (356.51) IU, with a range of 906 to 2180 IU. The mean (SD) duration of infusion was 3.7 (0.80) minutes, with a minimum of 2 minutes and a maximum of 5 minutes.

PK end points

The primary PK end point was assessed in the FAS. The 3 samples at preinfusion and 0 minutes postdose time points that constituted major protocol deviations were excluded from the main PK analyses. C1-INH activity increased from mean (SD) of 0.0841 (0.168) IU/mL before injection to 1.09 (1.1) IU/mL during injection and 0.826 (0.215) IU/mL at 15 minutes after injection, followed by a steady decline to 0.053 (0.109) IU/mL at 168 hours after injection (Fig 2, *A*).

C1-INH activity PK parameters for the FAS are presented in Table III. This analysis excluded a high proportion of individual patient data for AUC_{norm}, clearance, mean residence time, and volume of distribution because either the percentage of extrapolated AUC exceeded 20% of AUC_{inf} or the coefficient of regression was <0.70. Throughout this report, data are only shown where data for N > 1 patient were available and it was thus possible to perform statistical analyses.

The baseline-adjusted C1-INH activity over time for the FAS is shown in Fig E1 in the Online Repository at www.jaci-global.org. Median baseline-adjusted C1-INH activity increased from the adjusted preinjection value of 0 IU/mL at baseline to a mean (SD) value of 0.817 (1.08) IU/mL during injection and 0.623 (0.362) IU/mL at 15 minutes after injection, followed by a steady decline to 0.147 (0.346) IU/mL at 72 hours after injection and negative mean values thereafter. Baseline-adjusted C1-INH activity PK parameters are shown in Table E2 in the Online Repository.

Similar results were seen with C1-INH antigen as for C1-INH activity. Antigen concentration increased from a preinjection mean (SD) value of 0.1 (0.107) g/L to 0.216 (0.105) g/L during injection and 0.211 (0.0961) g/L at 15 minutes after injection, followed by a steady decline to 0.085 (0.0919) g/L at 168 hours after injection (Fig 2, *B*). C1-INH antigen PK parameters for the

TABLE IV. C1-INH antigen PK parameters of FAS of 20 patients

Parameter	No.	Mean (SD)	Median (range)	Geometric mean	Geometric mean CV (%)*
AUC_{last} (h•g/L)	20	20.7 (14)	16.2 (13.8-71.5)	18.5	43.4
C_{max} (IU/mL)	20	0.239 (0.1)	0.205 (0.15-0.54)	0.224	35.4
C_{max}/D (g/L/g)	20	0.718 (0.368)	0.655 (0.341-1.78)	0.655	43
$t_{½}$ (hours)	19	118 (76.4)	104 (46.9-416)	106	46.1
T_{max} (hours)	20	1.54 (2.38)	0.317 (0-6.1)	0.453	420

AUC_{last}, AUC from time of dosing to time of last measurable concentration; *C_{max},* maximum blood concentration; *CV,* coefficient of variation; *no.,* number of patients; *$t_{½}$,* half-life; *T_{max},* time to maximum concentration.
*Geometric CV (%) was calculated as [exp(SD2)−1]1/2×100, where SD was the standard deviation of the natural log-transformed data.

TABLE V. C4 antigen PK parameters of FAS of 20 patients

Parameter	No.	Mean (SD)	Median (range)	Geometric mean	Geometric mean CV (%)*
C_{max} (g/L)	20	0.129 (0.0467)	0.125 (0.07-0.27)	77.3	53.7
$t_{½}$ (h)	13	85.4 (34.8)	82.6 (27.5-134)	77.3	53.7
T_{max} (h)	20	53.7 (22.8)	59.4 (6-72.7)	44.3	93.8

C_{max}, Maximum blood concentration; *CV,* coefficient of variation; *no.,* number of patients; *$t_{½}$,* half-life; *T_{max},* time to maximum concentration.
*Geometric CV (%) was calculated as [exp(SD2)−1]1/2×100, where SD was the standard deviation of the natural log-transformed data.

TABLE VI. AEs of safety population of 20 patients

System organ class PT	Possibly or probably related, no. (%)*	Unlikely or not related, no. (%)	Total, no. (%) m
Any AE	2 (10.0)	5 (25.0)	7 (35.0) 10
Congenital, familial and genetic disorders	0	3 (15.0)	3 (15.0) 3
HAE	0	3 (15.0)	3 (15.0) 3
Musculoskeletal and connective tissue disorders	0	2 (10.0)	2 (10.0) 2
Back pain	0	1 (5.0)	1 (5.0) 1
Osteoporosis	0	1 (5.0)	1 (5.0) 1
General disorders and administration site conditions	1 (5.0)	0	1 (5.0) 1
Injection-site erythema	1 (5.0)	0	1 (5.0) 1
Infections and infestations	0	1 (5.0)	1 (5.0) 1
COVID-19	0	1 (5.0)	1 (5.0) 1
Investigations	1 (5.0)	0	1 (5.0) 1
Blood LDH increased	1 (5.0)	0	1 (5.0) 1
Nervous system disorders	0	1 (5.0)	1 (5.0) 1
Headache	0	1 (5.0)	1 (5.0) 1
Psychiatric disorders	0	1 (5.0)	1 (5.0) 1
Mixed anxiety and depressive disorder	0	1 (5.0)	1 (5.0) 1

AEs were coded using Medical Dictionary for Regulatory Activities, version 23.0. At each level of summation (system organ class and PT), patients who reported >1 event were included only once at each relationship. Percentages are based on total number of patients.
m, Number of events; *no.,* number of patients; *PT,* preferred term.
*Includes events with a missing relationship.

FAS are presented in Table IV. The analysis of C1-INH antigen excluded a high proportion of individual patient data for selected parameters because either the percentage of extrapolated AUC exceeded 20% of AUC_{inf} or the coefficient of regression was <0.70.

Median C4 activity over time is shown in Fig 2, *C.* C4 antigen concentration increased from a preinjection mean (SD) of 0.0482 (0.0238) g/L to a peak of 0.115 (0.0444) g/L at 72 hours after injection, followed by a decline to 0.072 (0.0409) g/L at 168 hours after injection. C4 antigen PK parameters for the FAS are presented in Table V.

When sensitivity analyses were performed using all samples, including those that constituted major protocol deviations, results were similar to those obtained when these samples were excluded and did not reveal any new interpretation of the data. Results were also similar for the per-protocol analysis set versus the FAS (data not shown).

Safety

The safety population consisted of all 20 patients enrolled in the study who received a single dose of the new C1-INH.

During the study, 7 patients experienced a total of 10 TEAEs (Table VI). Of these, 2 events in 2 patients, classed as mild in severity, were assessed as possibly related to the study drug by the investigator. These included 1 case of injection-site erythema that occurred on the day of C1-INH administration, which resolved on the same day, and 1 case of elevated lactate dehydrogenase (LDH) in a different patient. This patient had normal values at screening and on day 0, and the increased level (576 U/L; >2 times the upper limit of normal) was detected at the final visit, 14 days after administration of C1-INH. The increased level was reported as clinically significant; however, the central laboratory report stated that the sample was old and this finding might therefore have been an artifact. The event was confirmed to have resolved 16 days after the elevated LDH level by a

measurement performed by the local laboratory at the study center. This TEAE was not considered to be a severe AE. These cases were reviewed by the IDMC, which had no safety concerns.

No AEs of special interest were recorded during the study, no TEAEs were rated as severe or serious, and no TEAEs led to discontinuation of study drug or death. No pronounced changes over time were seen for any of the vital signs assessed, including pulse and respiratory rate, systolic and diastolic blood pressure, and body temperature.

No results from chemistry or hematology samples were considered clinically significant by the investigator. Blood samples were tested for the presence of anti–C1-INH antibodies on day 0 before the infusion of C1-INH and again at the final visit, and no patient had measurable antibody titers at either time point. For all serologic and virologic parameters tested, no patient who had a negative test result at baseline shifted to a positive result at the final visit.

DISCUSSION

PK results were obtained for all 20 patients who received C1-INH and were as expected. Although samples for 3 patients at 2 time points were excluded because of major protocol deviations, results were similar when all samples were included, confirming the validity of the PK results. No safety issues emerged in the study, and the new C1-INH was well tolerated.

The PK parameters of the new C1-INH were broadly in line with those of other C1-INH products.[22,23] The mean (SD) half-life of the new C1-INH in this study, when administered to patients with HAE at a dose of 20 IU/kg during an attack-free period, was 74.1 (19) hours when determined using C1-INH activity and 118 (76.4) hours when determined using an antigen assay. These values are higher numerically than those reported elsewhere in the literature for other pdC1-INH products. For example, in patients with HAE type I or II experiencing an acute abdominal or facial edema attack, the mean half-life of Berinert was 32.7 hours (90% confidence interval, 15.3-237.4 hours) when administered intravenously at 10 or 20 IU/kg,[22] and the mean (SD) half-life of Cinryze was 62.0 (65.59) hours when administered intravenously at 1000 IU (equivalent to 14 IU/kg for a 70 kg adult).[23] Van Doorn et al[24] demonstrated that PK parameters, including half-life, of the recombinant C1-INH Ruconest were dose dependent. Using nonlinear mixed-effects modeling and empiric Bayesian estimates, the half-life of recombinant C1-INH at a dose of 12.5 IU/kg was 40.1 minutes and at a dose of 25 IU/kg was 73.1 minutes. When taking dosing into account, the half-life of the new C1-INH remains numerically higher than that of other pdC1-INH products. Two factors known to influence the half-life of C1-INH include the severity of HAE in the patient population and whether the patients are currently experiencing an HAE attack.[23] Further studies are needed to confirm the validity of these results.

The new C1-INH was well tolerated. Only 2 TEAEs were considered by the investigator to be possibly related to study drug administration; these were injection-site erythema and elevated level of LDH, both of which were mild in severity and resolved. No TEEs were recorded during the study. Elsewhere, pdC1-INH has been shown to be well tolerated in long-term safety studies. In a postmarketing review that represented more than 570,000 treatments over a 26-year period, pdC1-INH (Berinert) was found to be well tolerated.[25] A total of 121 suspected adverse drug reactions were reported, including allergic or anaphylactic-type reactions (n = 12), fever and chills (n = 4), injection-site reactions (n = 2), and thrombosis (n = 16).[26] A registry that included 318 patients who received pdC1-INH (Berinert) for treatment of HAE attacks found that no AEs were reported among patients who received 1 or more doses of C1-INH. For 296 patients treated prospectively in the same study, 252 AEs were reported in 85 (28.7%) patients, including 2 TEEs, which were reported in subjects with thrombotic risk factors.

This study achieved the aims of determining the PK and safety of a new C1-INH in a rare disease setting. Limitations of the study include the small number of patients; however, this is due to the rarity of the disease. In addition, a high proportion of individual patient data for AUC_{norm}, clearance, mean residence time, and volume of distribution was excluded because either the percentage of extrapolated AUC exceeded 20% of AUC_{inf} or the coefficient of regression was <0.70. Where the limited number of patients for whom data were available meant that statistical analyses could not be performed, the data were not included in this analysis. Finally, there was a relatively high degree of variability seen in the PK parameters reported for C1-INH, which is consistent with previous reports.[22]

Conclusions

The PK parameters of the new C1-INH assessed in patients with C1-INH deficiency who were not experiencing HAE attacks were as expected and in line with those reported for other C1-INH concentrates in other studies. The new C1-INH administered by slow intravenous injection demonstrated a favorable safety profile and was well tolerated in this population. Further studies are warranted to determine the effectiveness and longer-term safety of new C1-INH in patients with HAE.

DISCLOSURE STATEMENT

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Key messages

- **OCTA-C1-INH is a new stable, virus-inactivated, nanofiltrated concentrate of C1-INH derived from human plasma.**
- **PK parameters of new C1-INH in patients with HAE were in line with those reported for other C1-INH concentrates.**
- **New C1-INH demonstrated a favorable safety profile in adult patients with HAE.**

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