

Safety, Pharmacokinetics (PK), and Pharmacodynamics (PD) of Subcutaneous (SC) CINRYZE® (C1 Esterase Inhibitor [Human]) with Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Hereditary Angioedema (HAE)

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ABSTRACT

Rationale: HAE manifests as recurrent painful, disabling, and sometimes fatal swelling attacks. CINRYZE administered by the IV route reduces edema and/or subcutaneous C1-INH and has proven efficacy and safety for both acute treatment and prevention. In order to provide broader options for patients to control disease, the potential enhancement of CINRYZE SC dispersion and absorption when co-administered with rHuPH20 was assessed in HAE patients.

Methods: This open-label, multiple-dose study was conducted in 12 HAE patients who received bi-weekly 1000 IU/2000 IU SC doses of CINRYZE co-administered as a single injection with rHuPH20 for 2 weeks. Comparisons were made to data from the same subjects who had prior exposure to CINRYZE without rHuPH20. Safety, tolerability, PK/PD, and immunogenicity were assessed.

Results: SC CINRYZE co-administered with rHuPH20 was well tolerated, with no AEs leading to discontinuation or SAEs. Moderate/severe injection site reactions were noted in the majority of subjects, with no erythema reported in 2 subjects. Co-administration with rHuPH20 resulted in increased CINRYZE systemic exposure relative to SC administration of CINRYZE alone. Preliminary mean values obtained were functional C1-INH exposure of 36.81 IU/mL, C_{max} of 0.43-0.72 U/mL, antigenic C1-INH level of 0.15-0.24 g/L, and CL was 174-270 mL/min. No subjects had detectable C1-INH antibodies in plasma 30 days after the last dose.

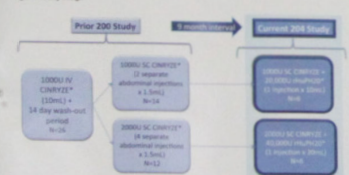
Conclusions: CINRYZE co-administered as a single SC injection with rHuPH20 was well tolerated and resulted in physiologically relevant functional C1-INH levels. Evaluation of the efficacy and safety of the innovative combination therapy is planned.

BACKGROUND

- HAE is a life-threatening, rare, and debilitating disease that manifests as recurrent, autosomal recessive subcutaneous swelling attacks due to a deficiency of C1 inhibitor (C1-INH).
- CINRYZE is a parenteral and non-refined, plasma-derived, intravenous (IV) formulation of C1-INH approved in the US for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE and in the EU for treatment, pre-procedure prevention, and routine prevention.
- rHuPH20 is a highly purified, recombinant human hyaluronidase which facilitates dispersion and absorption of co-administered products by temporarily reducing the viscosity of the subcutaneous matrix.
- Based on results from studies conducted with rHuPH20 and other injectable protein products, it is hypothesized that co-administration of rHuPH20 will increase dispersion and absorption of subcutaneously injected CINRYZE in order to achieve and maintain physiologically relevant levels of C1-INH functional activity.
- Subcutaneous (SC) administration of CINRYZE may fulfil an unmet medical need due to the limitations of IV administration in HAE patients.

METHODS

Figure 1. Study Design



*All doses were given twice weekly for 2 weeks

METHODS (CONT'D)

- Subjects in Study 204 received a total of 4 doses of CINRYZE with rHuPH20 on Days 1, 4, 8, & 11 during the study period.
- Safety was assessed by monitoring adverse events (AEs), changes in vital signs, and laboratory testing.
- Presence of C1-INH antibodies was assessed on Day 18 and 30 days after the last dose of study drug.
- Pharmacokinetic parameters:
 - Plasma C1-INH functional activity was assessed by chromogenic assays and plasma C1-INH antigenic concentration and C1 complement levels were assessed by ELISA.
 - Noncompartmental model analysis (WinNonlin 5.5) was performed on the concentration-versus-time data.
 - Parameters of interest: area under the curve of steady state PLC_{max} exposure at steady state considered between 0-96 h, C_{max} exposure at steady state, CL_{ss} , and relative bioavailability (F).

RESULTS

Table 1. Demographic and Clinical Characteristics of the Study Population

Parameter	CINRYZE 1000 IU/2000 IU SC + rHuPH20	CINRYZE 1000 IU/2000 IU SC + rHuPH20	All Subjects
Intention-to-Treat Safety Population, N	6	6	12
Age (years), Median (range)	32.9 (22, 45)	37.9 (18, 45)	36.9 (18, 45)
Gender, N			
Male	3	4	7
Female	3	2	5
Body weight (kg), Mean ± SD	70.6 ± 12.3	70.6 ± 12.3	70.6 ± 12.3
Body mass index (BMI), Mean ± SD	28.7 ± 7.7	28.6 ± 5.5	28.6 ± 6.6
Race, N			
White	5	6	11

SAFETY AND TOLERABILITY

- No subjects experienced a serious adverse event (SAE), or interrupted treatment or discontinued study drug due to an adverse event.
- No subjects receiving CINRYZE with rHuPH20 experienced an HAE attack during the study.
- No C1-INH antibodies were detected on Day 18 or 30 days after the last dose of CINRYZE with rHuPH20.

Table 2. Treatment Emergent Adverse Event (TEAE) Summary

Parameter	CINRYZE 1000 IU/2000 IU SC + rHuPH20	CINRYZE 1000 IU/2000 IU SC + rHuPH20	All Subjects
Intention-to-Treat Safety Population, N	6	6	12
Number of Subjects with at least 1 TEAE	6	6	11
Number of TEAEs related to study drug	6	6	11
Total Number of TEAEs	39	26	65
All TEAEs	39	26	65
TEAEs related to study drug	32	23	55
SAEs	25	13	38
Modestly Severe	11	8	19
Severe	2	2	4

*TEAE is defined as an adverse event with an onset day between study day 1 and study day 10.

- Injection site reactions accounted for all related treatment emergent adverse events:
 - 11 (92%) subjects experienced an injection site related adverse event.
 - Subjects most frequently reported injection site reactions (10/12) and/or pain (5/12).
 - Majority (57/61) of related TEAEs were "mild/moderate" in severity. 2 subjects (1) in each dosing arm each reported 2 events of "severe" erythema which did not interfere with study drug administration.

PHARMACOKINETIC RESULTS

- Mean plasma C1-INH functional concentration, as well as mean relative bioavailability and C1-INH functional parameters corrected for baseline values are presented in Table 3 and Figure 2 below.

Table 3. Mean Relative Bioavailability Derived from Baseline Corrected Values at Steady State (Outliers Excluded)

Parameter	CINRYZE 1000 IU/2000 IU SC + rHuPH20	CINRYZE 1000 IU/2000 IU SC + rHuPH20	CINRYZE 1000 IU/2000 IU SC + rHuPH20
C1-INH Functional F ₀ (95% CI)	44 (18)	48 (16)	55 (16)*
C1-INH Functional F ₀ (95% CI)	23-64	30-42	19-51
C1-INH Functional F ₀ (95% CI)	25-100	19-51	22-53
C1-INH Functional F ₀ (95% CI)	25-100	19-51	22-53

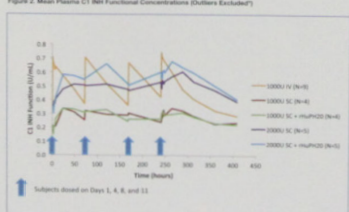
*Three subjects from 1 clinical site were excluded due to issues of sample handling. *F₀ is the ratio of the area under the curve (AUC) of rHuPH20 and rHuPH20 for a given concentration. F₀ relative bioavailability is 1.

Table 4. Mean C1-INH Functional Pharmacokinetic Parameters Derived from Baseline Corrected Values (SC) at Steady State (Outliers Excluded)

Parameter	CINRYZE 1000 IU/2000 IU SC + rHuPH20	CINRYZE 1000 IU/2000 IU SC + rHuPH20	CINRYZE 1000 IU/2000 IU SC + rHuPH20
C_{max} (U/mL)	0.473 (0.113)	0.208 (0.100)	0.242 (0.100)
C_{min} (U/mL)	0.228 (0.05)	0.126 (0.05)	0.175 (0.05)
AUC_{0-96h} (U·h/mL)	21.6 (4.8)	12.5 (7.9)	16.8 (8.3)
CL_{ss} (L/min)	174 (27)	174 (27)	174 (27)

*Three subjects from 1 clinical site were excluded due to issues of sample handling. *F₀ is the ratio of the area under the curve (AUC) of rHuPH20 and rHuPH20 for a given concentration. F₀ relative bioavailability is 1.

Figure 2. Mean Plasma C1-INH Functional Concentrations (Outliers Excluded)



*Three subjects from 1 clinical site were excluded due to issues of sample handling.

PHARMACOKINETIC RESULTS (CONT'D)

- It is theorized that to effectively prevent HAE attacks with CINRYZE, the regimen should result in sustained, physiologically relevant concentrations of C1-INH.
- A comparison of the time mean C1-INH concentrations versus time (0-4 U/mL) for CINRYZE and CINRYZE co-administered with rHuPH20 SC is presented in Figures 3 and 4.

Figure 3. Mean Percentage of Time C1-INH Functional Concentrations >0.4 U/mL at Steady State (All Subjects)

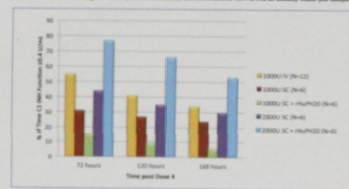
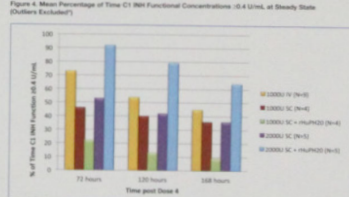
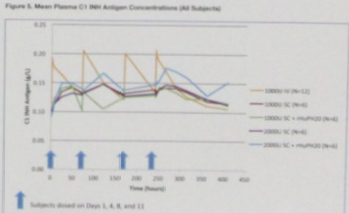


Figure 4. Mean Percentage of Time C1-INH Functional Concentrations >0.4 U/mL at Steady State (Outliers Excluded)



*Three subjects from 1 clinical site were excluded due to issues of sample handling.

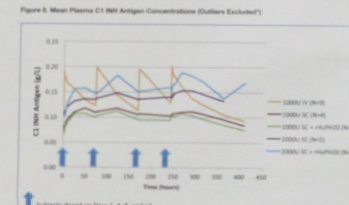
Figure 5. Mean Plasma C1-INH Antigen Concentrations (All Subjects)



Subjects based on Days 1, 4, 8, and 11.

PHARMACOKINETIC RESULTS (CONT'D)

Figure 6. Mean Plasma C1-INH Antigen Concentrations (Outliers Excluded)



*Three subjects from 1 clinical site were excluded due to issues of sample handling.

- C1 complement concentrations increased during the dosing period in all treatment groups.

DISCUSSION

- SC administration of CINRYZE with rHuPH20 offers a convenient method to self-administer CINRYZE every 3 or 4 days as a single injection.
- CINRYZE with rHuPH20 was well tolerated, mild to moderate injection site reactions were the most frequently reported AEs, with no SAEs or AEs leading to study drug discontinuation.
- CINRYZE with rHuPH20 delivers physiologically relevant C1-INH functional concentrations.
- CINRYZE 1000 IU/2000 IU SC with rHuPH20 resulted in mean C1-INH functional concentrations >0.4 U/mL for 92% of the 72-hour post-dosing period as compared to 73% for 1000 IU/2000 IU SC CINRYZE alone.
- Addition of rHuPH20 to CINRYZE 2000 IU/2000 IU SC resulted in a statistically significant increase in bioavailability of C1-INH antigen relative to CINRYZE 2000 IU/2000 IU SC alone.
- The addition of rHuPH20 to CINRYZE resulted in a dose proportionate increase of C1-INH function for C_{max} , C_{min} , and AUC_{0-96h} over the 1000-2000 IU SC dose range.
- Small sample size, time difference between analyses, and differences in drug administration variables may contribute to results observed among treatment arms.

CONCLUSION

- Subcutaneous injection of CINRYZE with rHuPH20 was easy to administer and well tolerated.
- CINRYZE 2000 IU/2000 IU SC with rHuPH20 resulted in physiologically relevant and sustained C1-INH functional concentrations >0.4 U/mL.
- This innovative combination of CINRYZE with rHuPH20 administered subcutaneously will be further evaluated for the prevention of HAE attacks.

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