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EMA/602545/2013
Committee for Medicinal Products for Human Use (CHMP)

Cinryze

(C1 inhibitor (human))

Procedure No: EMEA/H/C/001207/A46/0015.1

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I. EXECUTIVE SUMMARY

Final Study Report for Protocol 0624-200 was submitted in accordance with Article 46 of Regulation (EC) No 1901/2006.

Title of the study:
"An open-label, multiple-dose study to evaluate safety, pharmacokinetics, and pharmacodynamics of subcutaneous versus intravenous administration of CINRYZE in adolescents and adults with hereditary angioedema (Protocol 0624-2400)".

II. RECOMMENDATION

No regulatory changes are anticipated in Europe.

III. REGULATORY BACKGROUND:

Cinryze® [C1 esterase inhibitor (human)] is a highly purified, viral-inactivated, nanofiltered concentrate of C1 esterase inhibitor (C1 INH) produced from human plasma. C1 INH is a normal constituent of human blood and primarily regulates activation of the contact and complement pathways; C1 INH also regulates the fibrinolytic system.

Hereditary angioedema (HAE) is an autosomal dominant disease resulting from mutations of the C1 INH gene on chromosome 11 resulting in deficient and/or dysfunctional plasma C1 INH protein. The diagnosis of a C1 INH deficiency is suggested by a history that includes recurrent attacks of angioedema, characterized by swelling of the skin or mucosa. Serum C4, C1 INH antigen, and functional C1 INH levels can be measured to assist with the diagnosis of HAE.

CINRYZE intravenous (IV) formulation can be administered as replacement therapy of the deficient or dysfunctional C1 INH. CINRYZE was approved in the US for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE in 2008. CINRYZE was approved throughout the European Union (EU), via the Centralized Procedure, in 2011 for treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with HAE, and routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of HAE who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment. The approved dosing regimen of CINRYZE for routine prophylaxis against angioedema attacks is 1000 U administered IV every 3 or 4 days.

CINRYZE continues to be developed further for the treatment and prevention of angioedema attacks in patients with HAE (via IV and subcutaneous [SC] administration) and for use in clinical management of other disease states that may benefit from C1 INH administration.

The necessity to gain venous access for each IV administration can limit the use of CINRYZE by patients. Some HAE patients have inaccessible peripheral veins due to thrombophlebitis; others have veins of inadequate size or SC location. Moreover, because HAE patients are often subjected to chronic steroid use, many have an increased body mass index (BMI) which makes locating an accessible peripheral vein difficult. As a result, HAE patients often require placement of indwelling central venous catheters, which can be associated with complications. In addition, some patients with HAE may be reluctant or unable to administer CINRYZE via the IV route. Subcutaneous administration of CINRYZE represents an alternative method of administering prophylaxis that may fulfill an unmet medical need for HAE patients in whom accessing peripheral veins is difficult or central venous catheters are

contraindicated, and may alleviate potential complications associated with IV administration via indwelling catheters.

Protocol 0624-200 was developed to evaluate the SC route of administration, by comparing the pharmacokinetics, safety, and tolerability of CINRYZE following SC and IV administration in subjects with HAE. The doses of CINRYZE evaluated in this study were 1000 U administered IV (consistent with approved IV dosing regimen for HAE prophylaxis) and 1000 U or 2000 U administered by SC injection. Selection of doses for SC administration was based on results of the single-dose pilot healthy volunteer study (Protocol 0624-100) and volume considerations.

IV. SCIENTIFIC DISCUSSION

Study Design:

This open-label, multiple-dose study was conducted to evaluate the safety/tolerability and PK/PD of SC versus IV administration of CINRYZE in adolescent and adult subjects with HAE. The study was conducted at 6 centers in the US. Following a screening visit within 21 days prior to study entry, subjects with HAE who met all other specified entry criteria were randomly assigned to one of two treatment sequences:

- CINRYZE 1000 U IV→1000 U *via* SC injection (Sequence A/B)
- CINRYZE 1000 U IV→2000 U *via* SC injection (Sequence A/C)

Each subject was to participate in two 18-day treatment periods, which were separated by a washout period of at least 14 days (starting after Day 18 of Period 1) during which no C1 INH therapy or other blood products were administered. Study drug was administered twice weekly for 2 weeks (i.e., on Days 1, 4, 8, and 11) in each treatment period.In Period 1, all subjects were to receive 1000 U CINRYZE as an IV infusion of 10 mL over ~10 minutes (Treatment A); in Period 2, SC CINRYZE was to be administered at separate sites in the abdomen as either 2 x 1.5 mL injections (3 mL total; 1000 U, Treatment B) or 4 x 1.5 mL injections (6 mL total; 2000 U, Treatment C).

Subjects remained outpatient throughout the study. Eligible subjects reported to the study center on Day 1 of each treatment period (the day of the first CINRYZE dose in each period) and were to remain in the study unit until after collection of the 8 hour PK sample. Subjects were to return to the study unit on Days 2, 3, 4, 6, 8, 11 (additional 8- hour PK profile), 12, 13, 14, 16, and 18 of each treatment period for PK/PD and safety assessments. PK/PD evaluations included assessment of antigenic and functional C1 INH levels (PK) and C4 complement (PD) levels. Safety was monitored through the recording of adverse events (AEs) and changes in physical examinations, 12-lead electrocardiogram (ECG, performed if clinically indicated), vital signs, and clinical laboratory testing (complete blood count [CBC], blood urea nitrogen [BUN], and creatinine); blood samples were also analyzed for the presence of C1 INH antibodies (Days 1[pre-dose] and 18 of each treatment period).

Study personnel were to report any HAE attacks that occurred during the study as AEs, including those occurring during the washout period. General supportive care for management of acute HAE attacks (e.g., airway protection, IV fluids) was to follow standard practices at the investigational site or other site of care. If specific treatment with C1 INH was indicated (as determined by the investigator) the recommended treatment for use during the study was open-label CINRYZE 1000 U IV, followed by a second dose of 1000 U IV 1 hour later if needed.

If a subject had an HAE attack during Days 1-18 of one of the treatment periods, study treatment and study procedures were interrupted during that period. After recovery from the HAE attack, it was

possible for the subject to re-enter the study after at least a 14-day washout period in which no C1 INH therapy or other blood products were administered, if mutually agreed by both the Sponsor and investigator. Otherwise, the subject was discontinued from the study. If the subject had another HAE attack during either treatment period, the subject was discontinued from the study.

Study Period:

Initiation Date: 07 June 2010 (first subject dosed)
Completion Date: 16 December 2010 (last subject contact)

Main Criteria for Inclusion:

To qualify for enrollment, a subject had to:

- Be at least 12 years of age with a confirmed diagnosis of HAE and a history of at least one of the following:
    - C1 INH gene mutation
    - C4, C1 INH antigen, or functional C1 INH level below normal
- During the 3 consecutive months prior to screening, have a history of less than 1.0 HAE attack per month (average) treated with C1 INH therapy or any other blood products, ecallantide (Kalbitor®), icatibant (Firazyr®), antifibrinolytics (e.g., tranexamic acid), IV fluids, or narcotic analgesics.
- Have not received C1 INH therapy or any blood products (for treatment or prevention of an HAE attack) or ecallantide (Kalbitor®), icatibant (Firazyr®), or antifibrinolytics (e.g. tranexamic acid) within 14 days prior to the first dose of study drug in Period 1.
- Have had no change in androgen therapy (e.g. danazol, oxandrolone, stanozolol, testosterone) within 14 days prior to the first dose of study drug in Period 1.
- If female, agree not to start taking or change the dose of any hormonal contraceptive regimen or hormone replacement therapy (i.e. estrogen/progestin containing products) within 3 months prior to the first dose of study drug in Period 1.
- Have not received an immunization within 30 days prior to the first dose of study drug in Period 1.

Subjects:

Twenty-four (24) subjects were planned for enrollment. Twenty-six (26) subjects were randomized and treated with CINRYZE (any amount) and analyzed for safety: 26, 13, and 12 subjects received 1000 U IV, 1000 U SC, and 2000 U SC, respectively, and were included in the safety population. Twenty-five (25) subjects completed treatment (1 subject did not receive treatment with 1000 U SC in Period 2) and 24 subjects completed the study. Subjects with evaluable PK/PD profiles were included in the PK/PD analyses.

Two subjects had an HAE attack during Period 1 (IV) which resulted in an interruption of study drug and/or study procedures; per protocol, these subjects re-entered the study (Period 1) after the appropriate washout interval (2000408 and 2000702, Sequence A/B).

Treatments:

Subjects were treated 2 times/week for 2 weeks in each of two treatment periods (i.e. on Days 1, 4, 8, and 11 of Periods 1 and 2).

Study Drug, Dose and Mode of Administration:

CINRYZE was supplied as a lyophilized powder of 500 U (C1 INH)/vial for reconstitution with sterile water for injection. Subjects were to receive 1000 U IV CINRYZE in Period 1 and 1000 U or 2000 U SC CINRYZE in Period 2, according to their randomized treatment sequence (A/B or A/C):

• Treatment A - IV infusion (1000 U, 10 mL) over ~10 minutes.

• Treatment B - 2 x 1.5 mL SC injections (1000 U in 3 mL total; 2 separate abdominal injection sites).

• Treatment C - 4 x 1.5 mL SC injections (2000 U in 6 mL total; 4 separate abdominal injection sites).
Periods 1 and 2 were separated by a washout period of at least 14 days (with no C1 INH or other blood products).

Batches:

10A08L370A, 10A16L370A, 10B01L370A, 10D02L370A, 10D23L370A, 10E11L370A, 10E28L370A, 10F10L370A, and 10G09L370A

Methods of Evaluation:

Pharmacokinetic and pharmacodynamics parameters were calculated using observed or baseline-corrected concentrations versus actual time relative to Dose 1 of the treatment period and noncompartmental analyses in WinNonlin 5.3 (Pharsight, Cary, NC).

Efficacy: n/a

Safety was monitored by recording AEs and changes in physical examinations, 12-lead ECG (performed if clinically indicated), vital signs, and clinical laboratory testing.

Statistics

Pharmacokinetics and Pharmacodynamics – Plasma concentration data and PK/PD parameters were summarized using descriptive statistics and nominal times including number of observations (N), mean, standard deviation (SD), minimum (min), median, maximum (max), coefficient of variation (CV%), and geometric mean (PK/PD parameters only). Linear correlation coefficients were estimated for plots of C_{max}, R_{max}, C_{avg}, AUC_{0-72}, and $AUC_{0-\tau}$, values versus dose normalized to body weight (U/kg) values. Results of C1 INH antibody testing were reported for individual subjects, as appropriate.

Safety – Descriptive statistics (e.g., N, mean, standard error [SE], SD, median, range) were reported for baseline, post-baseline, and change from baseline values in clinical laboratory and vital signs parameters. Four summaries of AEs were presented by treatment period: all AEs, all AEs related to study drug, all treatment-emergent AEs (TEAEs), and all TEAEs related to study drug. Adverse events were coded using MedDRA (Medical Dictionary for Regulatory Activities) Version 14.0.

Study Population and Demographics:

Randomized and treated subjects, N=26

Gender = Females, 15 (58%); Males, 11 (42%)

Race = White/Caucasian, 22 (85%); Black/African American, 4 (15%) Ethnicity = Hispanic/Latino, 1 (4%); Not Hispanic/Latino, 25 (96%)

Age (Mean ± SD): 32.7 ± 14.7 years; 4 subjects <18 years of age (range: 12-16 years)

Mean BMI: Females: 26.6 kg/m², Males: 31.3 kg/m²

Conduct of the study:

25 (96%) Subjects completed treatment and 24 (92%) subjects completed the study.

14 subjects were randomized and treated into Sequence A/B (1000 U IV/1000 U SC); 13 (93%) completed treatment and 12 (86%) completed study. One subject (Subject 2000702) did not complete the study or treatment (participated in IV period only) due to an AE (HAE attack); one additional subject did not complete the study due to an AE (HAE attack, Subject 2000202).

12 Subjects were randomized and treated Sequence A/C (1000 U IV/2000 U SC); all 12 completed treatment and study.

Results:

Pharmacokinetic Results:

Plasma concentration versus time profiles of antigenic and functional C1 INH following IV administration of CINRYZE were characterized by a typical pronounced ratio of peak to trough concentrations.

PK-results for the IV administration have been provided in a table, below:

Steady-State (Day 11) Pharmacokinetic Parameters of C1 INH Antigen and Functional C1 INH Activity in Subjects with HAE		
	Parameter	**CINRYZE 1000 U IV**
C1 INH Antigen	C_{max} (g/L)	0.100 ± 0.033
	C_{avg} (g/L)	0.049 ± 0.021
	AUC_{0-72} (g*h/L)	3.77 ± 1.56
	AUC_{0-} (g*h/L)	4.08 ± 1.74
	K_{el} (h^{-1})	0.02 ± 0.01
	$t_{½}$ (h)	42.8 ± 24.1
	Cl_{ss} or Cl_{ss}/F (mL/h/kg)	0.71 ± 0.62
	V_z or V_z/F (mL/kg)	35.8 ± 21.0
	F (%)	N/A
Functional C1 INH Activity	C_{max} (U/mL)	0.45 ± 0.14

	C_{avg} (U/mL)	0.23 ± 0.10
	AUC_{0-72} (U*h/mL)	17.7 ± 7.8
	AUC_{0-} (U*h/mL)	19.2 ± 8.8
	K_{el} (h^{-1})	0.02 ± 0.01
	$t_{½}$ (h)	51.7 ± 29.2
	Cl_{ss} or Cl_{ss}/F (mL/h/kg)	0.86 ± 0.64
	V_z or V_z/F (mL/kg)	52.5 ± 24.3
	F (%)	N/A

The level of plasma C1 INH that effectively prevents HAE attacks varies between patients. Within-patient factors may also influence disease severity and response to therapy, and disease severity can fluctuate over time. Consequently, a simple PK association between plasma C1 INH concentrations and efficacy in this complex and dynamic condition has not been established. As a result, response to therapy continues to be reliant on clinical measures and based on the results of the randomized and open-label prevention studies with CINRYZE, employing the recommended IV dose of 1000 U every 3 or 4 days is an effective regimen.

Pharmacodynamic Results:

The results from this repeat-dose PK/PD study in HAE patients suggest that, despite the high degree of inter-subject variability, exposure to C1 INH antigen and functional C1 INH activity, as measured by mean (± SD) steady-state baseline-corrected C_{avg} and AUC_{0-T}, achieved following SC administration of 2000 U was similar to that following IV administration of 1000 U. In addition, the PD response at steady-state, i.e., the R_{max} and AUC_{0-T} for C4 complement following SC administration of 2000 U was similar to that following IV administration of 1000 U. The IV results are presented in the table below.

Steady-State (Day 11) Pharmacokinetic Parameters of C4 Complement in Subjects with HAE	
Parameter	**CINRYZE 1000 U IV**
R_{max} (mg/L)	71 ± 31
AUC_{0-72} (mg*h/L)	3870 ± 1994
AUC_{0-T} (mg*h/L)	4411 ± 2308

Data were available from 4 subjects less than 18 years of age and 21 subjects $\geq$ 18 years of age. Considering the small sample size and inherent inter-subject variability, mean change from baseline levels and derived PK/PD parameters were generally similar in both groups. Similarly, there were no obvious differences in complement levels or PK/PD parameters due to gender or body weight.

Safety Results:

No deaths or other serious adverse events (SAEs) occurred during the study. One subject (2000702) had study drug discontinued due to an AE (HAE attack, onset Day 16 of Period 1 re-entry [1000 U IV]). One additional subject (2000202) was prematurely discontinued from the study due to an AE (HAE

attack) which occurred 3 days after completing treatment with 1000 U SC in Period 2. No subjects experienced a TEAE that was thrombotic or thromboembolic in nature during the study.

Across all subjects, 85% (22/26) reported 1 or more TEAEs during the study: 46% (12/26) of subjects receiving 1000 U IV, 77% (10/13) of subjects receiving 1000 U SC, and 92% (11/12) of subjects receiving 2000 U SC. During the IV period, the only TEAE reported in more than 1 subject was angioedema attack due to HAE (19%, 5/26).

Overall, subjects ≥18 years of age reported more TEAEs compared to subjects <18 years of age. Both cohorts reported injection site reactions, with pain followed by erythema being most prominent in frequency. There were no other notable differences.

Results of clinical laboratory evaluations and vital signs measurements were generally unremarkable and did not suggest any treatment-emergent abnormalities related to the administration of CINRYZE.

Immunogenicity: For each treatment period, plasma samples collected on Day 1 (pre-dose) and on Day 18 (168 h post Dose 4) were analyzed for C1 INH antibodies. One subject (Subject 2000203) was not tested at pre-dose of Treatment Period 1 due to insufficient plasma sample volume. In addition to the scheduled testing, Subject 2000402 was inadvertently tested at 8 h post-Dose 1 of Period 1. No subjects had detectable C1 INH antibodies.

Conclusions:

- CINRYZE administered via the SC route at doses of 1000 U and 2000 U was associated with generally mild to moderate injection site reactions, most notably pain, which was commonly characterized as burning or stinging. No subjects were discontinued from study drug due to an injection site reaction.
- There were no clinically significant safety signals due to CINRYZE on laboratory parameters or vital signs.
- No subjects had detectable C1 INH antibodies in plasma samples collected on Day 1(pre-dose) and on Day 18 (168 h post Dose 4) of each treatment period.
- Mean change from baseline levels of C1 INH antigen, functional C1 INH activity and C4 complement, and the derived PK/PD parameters were generally similar in 4 subjects <18 years of age compared with 21 subjects ≥18 years of age. There were no obvious differences in complement levels or PK/PD parameters due to gender or body weight.

V. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION

The MAH submitted a Final Study Report regarding study 0624-200 providing PK/PD and safety-results on a comparative clinical study with Cinryze in two application-forms (i.v. versus s.c.) and two dosages (1000 versus 2000 U) in accordance with Article 46 of Regulation (EC) No 1901/2006.

Within the study, 26 subjects were treated, 4 of them were <18 years of age.

The submitted clinical expert report according to article 46 mainly reflects PK/PD and safety results over all available subjects. Comparative presentation and characterization of the adolescent subgroup has not been provided.

It is acknowledged that low number of included subjects, overall (26), and the even lower number of adolescent subjects (4) does not allow valid comparative analysis. However, demographic data, treatments, and study results of this subgroup in comparison with adults are considered to form the basis for evaluation and conclusions. Raw data regarding PK/PD are available within the Clinical Study Report (Tables 10) which might serve as a data-base for comparative analysis. Subject-characterization and comparative safety analysis are required, in addition.

REQUEST FOR SUPPLEMENTARY INFORMATION

The MAH is requested to submit within 4 weeks a response on the following Clinical Issues:

Low number of included subjects, overall (26), and the even lower number of adolescent subjects (4) does not allow valid comparative analysis. However, demographic data, treatments, and study results of this subgroup in comparison with adults are considered to form the basis for evaluation and conclusions. Raw data regarding PK/PD are available within the Clinical Study Report (Tables 10) which might serve as a data-base for comparative analysis. Subject-characterization and comparative safety analysis are required, in addition.

The MAH is requested to provide further comparative data and to comment on:

- Characterization of the adolescent subgroup including demographic data
- Characterization of the adolescent subgroup regarding applied treatments
- PK-data analogue to the above presented Pharmacokinetic Parameters covering two age groups (adults ≥ 18 years and adolescents 12-18 years), comparatively and reflecting baseline-corrected medians (ranges) for antigen and functional activity of C 1 INH.
- comprehensive safety data of the adolescent subgroup.
- 5 of 26 subjects were reported with HAE attacks after the IV treatment which is considered to be surprising. Number of adolescents within this group is requested.

VI. ASSESSMENT OF THE RESPONSES TO RSI

Question

Low number of included subjects, overall (26), and the even lower number of adolescent subjects (4) does not allow valid comparative analysis. However, demographic data, treatments, and study results of this subgroup in comparison with adults are considered to form the basis for evaluation and conclusions. Raw data regarding PK/PD are available within the Clinical Study Report (Tables 10) which might serve as a data-base for comparative analysis. Subject-characterization and comparative safety analysis are required, in addition.

The MAH is requested to provide further comparative data and to comment on:

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- Comprehensive safety data of the adolescent subgroup.

- 5 of 26 subjects were reported with HAE attacks after the IV treatment which is considered to be surprising. Number of adolescents within this group is requested.

MAHs response (Summary)

Within eCTD sequences 046 and 048 the MAH submitted supplemental data regarding the adolescent sub-population of the study. Demographic characteristics and applied treatment schedules were amended. Furthermore, comparative pharmacokinetic parameters for the antigen and functional C1 INH activity have been provided. Safety analysis with a focus on the adolescent subgroup has been compiled which covers frequency of angioedema attacks.

Tables on demographic details, frequency of HAE attacks, and comparative safety-analyses are included in the response document, and references to the CSR have been provided.

Occurrence of angioedema attacks with regard to the adolescent subject group has been further elucidated:
The proportion of subjects who experienced an angioedema attack during the IV treatment period was similar for subjects <18 years of age (1/4, 25%) and subjects ≥18 years of age (4/22, 18%). However, all but 1 of these subjects (a 48-year-old female) experienced the attack(s) 4-7 days **after** dosing with IV CINRYZE was completed. Individual reports of concerned subjects have been provided. One of 4 subjects <18 years of age (25%) and 1/21 subjects ≥18 years of age (5%) experienced an angioedema attack during the SC treatment period. Individual reports of the concerned subjects have been provided.

Assessment of MAHs response

Requested details regarding the adolescent subgroup from study 0624-200 have been submitted within the response document. Details, analyses, and tables cover the identified gaps as identified in the assessment report. Furthermore, the results do not point to specific efficacy or safety issues within this sub-population. Comparative PK-data show slightly decreased AUC and c_{max} and increased t_{max} and $t_{1/2}$. Clearance might be interpreted as slightly increased in the adolescent population. However, these differences are considered to be marginal and not representative with respect to the low subject numbers. Description of the episodes of HAE attacks has been provided. As those episodes represent an anticipated pattern and mainly evolved 5 - 7 days after treatment and as frequency and character of the attacks in adolescents did not differ from the adults, no signal has been detected at that point.

Conclusion

The submitted supplemental comparative analysis regarding 4 out of 26 subjects is considered to cover the raised open issue, adequately.

VII. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

The MAH submitted a Final Study Report regarding study 0624-200 providing PK/PD and safety-results on a comparative clinical study with Cinryze in two application-forms (i.v. versus s.c.) and two dosages (1000 versus 2000 U) in accordance with Article 46 of Regulation (EC) No 1901/2006.

Within the study, 26 subjects were treated, 4 of them were <18 years of age.

The submitted clinical expert report according to article 46 mainly reflects PK/PD and safety results over all available subjects. It is acknowledged that low number of included subjects, overall (26), and the even lower number of adolescent subjects (4) does not allow valid comparative analysis. Comparative presentation and characterization of the adolescent subgroup have been addressed, adequately.

Based on the respective data, no regulatory action with respect to the currently valid SmPC is recommended.

Recommendation

☒ PAC fulfilled (all commitments fulfilled) - No further action required