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EMA/175539/2013
Committee for Medicinal Products for Human Use (CHMP)

Cinryze

(C1 inhibitor (human))

Procedure No: EMEA/H/C/001207/A46/0014

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 0624-400 was submitted in accordance with Article 46 of Regulation (EC) No 1901/2006.

Title of the study:
"A phase 4 study to evaluate the safety and effect of escalating doses of CINRYZE® (C1 inhibitor [human]) as prophylactic therapy in subjects with inadequately controlled hereditary angioedema attacks (Protocol 0624-400)".

II. RECOMMENDATION

No SmPC and PL changes are proposed.

III. REGULATORY BACKGROUND

As a condition of CINRYZE approval October 2008 in the US for routine prophylaxis against angioedema attacks in patients with HAE, ViroPharma conducted Protocol 0624-400 as a post licensure requirement study with a commitment of submitting the clinical study report October 2012. The purpose of this study was to evaluate the safety and treatment effect of escalating doses of CINRYZE. The original PIP application for CINRYZE did not include this protocol, but, at the request of the PDCO, it was added with a specific requirement to enrol 6 children.

Recruitment into Protocol 0624-400 proved challenging due to few patients failing to respond to the approved preventive dosing regimen of CINRYZE and this proved even more challenging for children. Based on the diligent efforts to identify and enrol paediatric subjects in this study in the US, which included contacting 63 centres treating paediatric patients, it was not feasible to enrol six paediatric patients who were failing to respond adequately to CINRYZE within any foreseeable timeframe. Despite these substantive recruitment efforts no children < 12 years of age were enrolled; only one 16 year old was enrolled.

A request for a modification was made by ViroPharma to remove this study from the PIP to enable it to be closed and reported to the FDA as required by US law (Food and Drug Administration Amendments Act of 2007). The PDCO did not agree with the proposed modification without "addressing the gap in paediatric information through other measures". ViroPharma was advised to "address the PDCO's concerns in a new modification procedure by providing sufficient data and/or amending their paediatric clinical development programme accordingly." In response, ViroPharma has submitted a new request for modification to delete Protocol 0624-400 from the PIP and replace with a new paediatric study (Protocol 0624-207). This study will evaluate the safety and tolerability, treatment effect and immunogenicity of CINRYZE IV for the prevention of angioedema attacks in children 6-11 years of age.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

CINRYZE® 500 Units is provided as powder and solvent for solution for injection.

CINRYZE® (C1 esterase inhibitor [human]) consists of a protein fraction prepared from human plasma. The manufacturing process includes 3 virus inactivation/removal steps: PEG precipitation,

pasteurization, and nanofiltration. C1 esterase inhibitor is a normal human plasma protein that is not subject to Cytochrome P450 metabolism, excretion, or PK drug-drug interactions exhibited by low molecular weight compounds.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a study report with only one paediatric patient of 16 years amongst 20 included subjects.

2. Clinical study

➢ Description

This open-label, multicenter, Phase 4 study assessed escalating doses of IV CINRYZE (1500 U, 2000 U, and 2500 U) as prophylactic therapy to lower the angioedema attack rate in subjects who were not adequately controlled while receiving the recommended CINRYZE dosing regimen (1000 U every 3 to 4 days via IV injection).

➢ Methods

- Objective(s)

The objectives of this study were: (1) to assess the safety and tolerability of escalating doses of CINRYZE; (2) to assess the effect of an escalating dose algorithm for CINRYZE on angioedema attack rates; and (3) to assess the immunogenicity of CINRYZE.

- Study design

Open-label multicenter Phase 4 study

First subject was dosed 31Aug2009 and last subject contact was 24May2012. Subjects with qualifying angioedema attack rates, and who met other specified entry criteria, were entered into a 3-step dose-escalation algorithm. Each step consisted of 12 weeks of initial monitoring of subject safety while receiving the escalated prophylaxis therapy dose, followed by computation of the average monthly attack rate based on subject reports of any angioedema attack (regardless of intensity) and the actual duration of therapy for that step.

- Diagnosis and main criteria for inclusion

To qualify for enrollment, a subject had to:

- Be ≥6 years of age and ≥25 kg body weight.

- Have a confirmed diagnosis of HAE with a documented history of swelling of the face, extremities, gastrointestinal tract, genitalia, or larynx and a history of at least one of the following:

  - C1 inhibitor (C1 INH) gene mutation
  - C4 level below the lower limit of the reference range
  - C1 inhibitor antigen level below the lower limit of the reference range
  - Functional C1 inhibitor level below the lower limit of the reference range
  - Family history of HAE (i.e., grandparent, parent, sibling)

- Have a history of >1.0 angioedema attack per month (average) of any severity during the 3 consecutive months prior to screening while receiving the recommended CINRYZE dosing of 1000 U every 3 to 4 days via IV injection.

- Have not had a history of abnormal blood clotting or other coagulopathy.

- Have not received any blood products (other than CINRYZE) within 60 days prior to screening.

- Study population

Enrolled and treated subjects, N=20

Gender=Females, 14 (70%); Males, 6 (30%)

Race=White/Caucasian, 18 (90%); Black/African American, 1 (5%); Other (Mexican), 1 (5%)

Ethnicity=Hispanic/Latino, 2 (10%); Not Hispanic/Latino, 18 (90%)

Age (Mean ± SD): 41.7 ± 15.3 years (range: 16-77 years)

- Number of subjects (planned and analysed)

Twenty (20) subjects were planned for enrollment. Twenty (20) subjects were enrolled and treated with IV CINRYZE and analyzed for safety.

- Treatments

Duration of treatment was 2 times/week for 12 weeks in each dose-escalation step (Steps 1-3) and 2 times/week for 3 months in the follow-up period.

20 subjects received 1500 U CINRYZE in dose-escalation Step 1; 13 subjects were dose-escalated to Step 2 and received 2000 U CINRYZE, 12 of whom were dose-escalated to Step 3 and received 2500 U CINRYZE. Sixteen (16) subjects (80%) completed treatment and 17 subjects (85%) completed the study.

- Outcomes/endpoints

Efficacy assessments included the following: Incidence of any angioedema attacks as determined by subject reported diary data, use of rescue therapy, hospitalization, and/or use of other therapy for treating an angioedema attack (e.g., androgens). Angioedema attacks included the following: (1) any attack of swelling or pain typical of an HAE event and subsequently recorded by the subject, study personnel, or home health care professionals, and (2) Actionable attacks, where “Actionable” was defined as seeking medical attention including any of the following interventions: IV fluids, narcotics, plasma administration, or C1 INH therapy.

A subject was deemed a “success” (an average of ≤1.0 angioedema attack/month) at the most recent dosing step and the investigator and medical monitor determined that it was safe for the subject to continue on that dose. This subject entered the 3-month follow-up period at that dose level with continued safety monitoring.

The subject could not re-enter the study for purposes of dose escalation during any “follow-up” period.

A subject was deemed a “failure” (an average of >1.0 angioedema attack/month), and the next higher step of the dose-escalation algorithm was initiated for that subject provided that the investigator and medical monitor agreed that the subject was sufficiently compliant and that dose escalation was appropriate.

After a minimum of 6 months for those adequately controlled on the entry dose of this study (1500 U twice per week) and a maximum of 12 months of enrollment for subjects reaching the third tier of dose escalation (2500 U twice per week), subjects completed the study and their follow up was referred to the physician who managed their HAE care.

If four (or more) patients were deemed to have achieved successful control, the study was declared a success.

Safety was monitored through the recording of AEs and any changes in physical examinations, vital signs, and clinical safety laboratory testing. Confirmed diagnoses of clinically significant thrombotic or thromboembolic events were to be reported as serious adverse events.

- Statistical Methods

Safety: Descriptive statistics (e.g., N, mean, SE, SD, median, range) were reported for baseline, post-baseline, and change from baseline values in clinical laboratory (testing performed pre-dose on Day 1 of dose escalation Step 1 [baseline] and at Week 12 and follow-up Month 3 for each dose level) and vital signs (BP and HR measured immediately before and approximately 15 minutes after completion of each injection) parameters. Two summaries of AEs were provided: all treatment-emergent AEs (TEAEs) and all TEAEs related to study drug.

Adverse events were coded using MedDRA (Medical Dictionary for Regulatory Activities) Version 15.0.

Efficacy: In this study, the calculation of angioedema attack rates included all reported attacks, regardless of severity, whether Actionable or not. Subject-reported HAE symptoms that occurred on consecutive days constituted one angioedema attack. The attack rate for a therapy period, nominally 84 days (12 weeks), was normalized to a monthly attack rate using the following formula:

Monthly attack rate = 30.4 x (# angioedema attacks in period) / (# days monitored in period)

Thus, the calculated attack rate was based only on the formal observation interval (during which attacks were explicitly monitored). This same calculation was performed for Actionable attacks by substituting for the numerator the number of Actionable attacks in the observation period. Subjects observed to have an average monthly attack rate of ≤1.0 per month at the end of any step (Week 12) were deemed a “success” based on the protocol definition.

➢ Results

- Recruitment/ Number analysed

Twenty subjects were enrolled and treated with IV CINRYZE and analyzed for safety: 20 subjects received 1500 U CINRYZE in dose-escalation Step 1; 13 subjects were dose-escalated to Step 2 and received 2000 U CINRYZE, 12 of whom were dose-escalated to Step 3 and received 2500 U CINRYZE. Sixteen (16) subjects (80%) completed treatment and 17 subjects (85%) completed the study. The study population was composed of 14 (70%) females and the majority of subjects were white 18 (90%). The mean age (± SD) was 41.7 ± 15.3 years (range: 16-77 years).

- Efficacy results

All subjects enrolled in this study (n=20) had recurrent angioedema attacks despite therapy with CINRYZE 1000 U IV twice weekly; notably 3 of these subjects were receiving CINRYZE 1000 U IV thrice weekly. All of these refractory subjects started the study at an IV CINRYZE dose of 1500 U (Step 1); 13 subjects were dose escalated to 2000 U (Step 2), 12 of whom were further dose escalated to 2500 U (Step 3). Nine (45%) of the 20 subjects were deemed a success based on the protocol definition (i.e., an average of ≤1.0 angioedema attack/month at the end of any step [Week 12]) and continued

on their final CINRYZE dose during follow-up at the investigator's discretion: 4 subjects at Step 1 (1500 U) and 5 subjects at Step 3 (2500 U). Of note, 1 of these subjects was also a success at Step 2 (2000 U), based on the protocol definition; however, this subject was dose-escalated to Step 3, at the investigator's clinical discretion. As outlined in the protocol efficacy assumptions, this study can be declared a success because greater than 4 subjects had an average of ≤1.0 angioedema attacks/month at the end of any step.

2 subjects had angioedema attack rates slightly above the limits of protocol defined success at their final dose level and continued on their final dose during follow-up at the investigator's discretion: 1 subject at Step 1 (1500 U) and 1 subject at Step 3 (2500 U) had monthly average attack rates of 1.4 and 1.8, respectively.

3 further subjects were found with a reduction from historical angioedema attack rate of >1 at the end of any step (Week 12): 1 subject at Step 1 (1500 U) and 2 subjects at Step 3 (2500 U).

Overall, 11 (55%) of 20 subjects were deemed clinical failures (i.e., an average of >1.0 angioedema attack/month at the end of any step [Week 12]). Of note, 2 of these 6 subjects prematurely discontinued treatment and study: 1 subject during Step 1 (received only 9 doses of study drug); and 1 subject during Step 2 (received only 9 doses of study drug during Step 2).

- Safety results

No deaths were reported during this study.

Two subjects experienced SAEs during the study; however, these events were considered by the investigator to be unrelated to study drug (cerebral hygroma for 1 subject; and HAE [verbatim: laryngeal angioedema attack], anemia [verbatim: anemia (worsening)], and bile duct stone [verbatim: worsening choledocholithiasis] for 1 subject). One of these subjects had study drug interrupted due to 2 SAEs while receiving 2000 U CINRYZE (due to hospitalization).

No subject was discontinued from escalating doses of IV CINRYZE up to 2500 U due to an AE.

No subjects experienced a systemic thrombotic or thromboembolic TEAE during the study.

90% of all subjects (18/20) reported 1 or more TEAEs during the study: 75% (15/20) of subjects receiving 1500 U CINRYZE, 85% (11/13) of subjects receiving 2000 U CINRYZE, and 92% (11/12) of subjects receiving 2500 U CINRYZE. The most frequently reported TEAE following IV injection of CINRYZE across all dose levels was URTI, reported by 25% (5/20) of all subjects, followed in overall frequency by nasopharyngitis, reported by 15% (3/20) of all subjects.

The majority of TEAEs in this study (95%, 86/91 events) were considered by the investigator to be unrelated to study drug; 2 (10%) of the 20 subjects had a total of 5 events that were considered related to CINRYZE: catheter site pain (1 event at 1500 U, 1 event at 2500 U), dyspnea (2500 U, Day 173), and medical device complication (verbatim: blood clot in port; 1500 U, onset Day 81), reported by 1 subject and muscle spasms (2000 U, also related to concomitant medication for pre-existing chronic myeloid leukemia [CML]) reported by 1 subject. The medical device complication (blood clot in port) was treated locally with streptokinase with complete resolution.

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.

C1 INH antibodies (inhibitors): Two subjects who had progressed through dose escalation Steps 1-3 (1500, 2000, and 2500 U, respectively) had C1 INH antibodies detected in plasma samples collected during the study. Both were deemed clinical failures.

One subject had C1 INH antibodies detected at baseline (pre-dose Day 1) and in all samples collected at Week 12 of Steps 1 (1500 U), 2 (2000 U), and 3 (2500 U), respectively. The other subject had no detectable C1 INH antibodies at baseline (pre-dose Day 1), or at Week 12 of Step 1 (1500 U) and Step 2 (2000 U); subsequently, C1 INH antibodies were detected (ratio of 5.6) in the plasma sample collected at Week 12 of Step 3 (2500 U). An evaluation is ongoing to further characterize these C1 INH antibodies. No other subjects had detectable C1 INH antibodies in any of the samples analyzed.

- Data regarding paediatric subjects

The only pediatric subject enrolled in the study was a 16 year old male subject with a 4 year diagnosis of HAE. At baseline, he had a historical monthly attack rate of 11 and missed approximately 20 days of school per month. During the first dose escalation step (1500 U) he experienced 11 attacks over 83 days and had a reduction in monthly attack rate to 1.7 (based on 181 days of follow-up). At the end of Step 1, the subject prematurely discontinued treatment on Day 83 and subsequently withdrew from the study at the investigator/sponsor discretion due to travel outside of the USA. The patient received a total of 24 CINRYZE doses which were well tolerated.

3. Discussion on clinical aspects

The Clinical Study Report of study 0624-400 has been submitted in accordance with Article 46 of Regulation (EC) No 1901/2006. The only included paediatric subject (ID 4001004) was prematurely discontinued from the study at the end of Step 1 (1500 U) dose-escalation. No individual data has been provided regarding efficacy and safety. According to the expert statement all doses in this patient were well tolerated.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

Overall, results of that documentation do not add relevant information regarding paediatric use to be reflected in the currently valid SmPC regarding paediatric use.

We recommend supplementation of the appendices including Patient data listings (CSR 0624-400, Section 16) for completeness of the documentation in the frame of future submissions affected by study 0624-400.

➢ Recommendation

No further regulatory action is considered to be required.