London, 22 June 2017
EMA/386239/2017
Committee for Medicinal Products for Human Use (CHMP)

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

Cinryze

C1-esterase inhibitor, human

Procedure no: EMEA/H/C/001207/P46/017

Note

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

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1. Introduction

On 24 March 2017, the MAH submitted the final report for study SHP616-401 in accordance with Article 46 of Regulation (EC) No 1901/2006.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

CINRYZE is a highly purified, viral-inactivated, nanofiltered concentrate of C1 INH produced from human plasma. C1 INH is a normal constituent of human blood.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for:

Study SHP616-401- *A European Multicenter, Multicountry, Postauthorisation, Observational Study (Registry) of Patients With Hereditary Angioedema (HAE) Who Are Administered CINRYZE® (C1 Inhibitor [Human] for the Treatment or Prevention of HAE Attacks*

One pediatric patient was treated with CINRYZE during Study 616-401.

Shire Study SHP616-401 was an observational (non-interventional) study conducted to characterize the safety and use of CINRYZE in routine clinical practice in patients with HAE who received CINRYZE for prevention and/or treatment of angioedema attacks.

The objectives of the study were:

- To characterize the safety and use of CINRYZE in routine clinical practice when administered for routine prevention of angioedema attacks, pre-procedure prevention of angioedema attacks, and/or treatment of angioedema attacks.

- To monitor severe attacks and laryngeal attacks, as well as cases in which treatment with CINRYZE is initiated more than 4 hours after onset of an attack.

2.3.2. Registry-study SHP616-401 as submitted by the MAH

CINRYZE® (C1 inhibitor [human]) has been developed for the management of angioedema attacks in patients with C1 inhibitor (C1 INH) deficiency (ie, Type I and II hereditary angioedema [HAE]). Administration of CINRYZE increases serum C1 INH levels, replacing the deficient C1 INH activity in HAE patients, and restoring the natural regulation of the contact, complement, and fibrinolytic systems, thereby controlling swelling or the propensity to swell.

CINRYZE has marketing authorization in 36 countries. In June 2011, IV administration of CINRYZE was approved by the European Medicines Agency (EMA) for the treatment, routine prevention, and pre-procedure prevention of angioedema attacks in adults and adolescents (12 to 17 years old) with HAE.

In June 2016, the marketing authorization holder (MAH) submitted variation EMEA/H/C/001207/II/0045 to extend the indication "treatment and pre-procedure prevention of angioedema attacks" to 2 years and above and extend the indication "routine prevention of angioedema attacks" to 6 years and above. The variation received a positive opinion from the CHMP on 15 Dec 2016 and a European Commission's decision on 26 Jan 2017 approving the extended indications.

Following discussions with the EMA, ViroPharma SPRL (now part of Shire), sponsored a postmarketing registry to provide additional data on the safety and the use of CINRYZE in the European Union (EU) (follow-up measure [FUM] 005). As part of variation EMEA/H/C/001207/II/0039, the EMA agreed that Study 0624-401 (Study SHP616-401) could be discontinued (reason: low enrolment) and would be replaced by the ICATIBANT Outcome Survey (IOS) registry.

The patients enrolled up to the time point of last-patient-first-visit of the CINRYZE registry, were to be followed up for 12 months, as described in the CINRYZE registry protocol. After this time point, new patients on CINRYZE will be enrolled in IOS registry, if they consent.

Currently approved indication is:

- Treatment of angioedema attacks in adults, adolescents, and children (2 years old and above) with HAE.
- Routine prevention of angioedema attacks in adults, adolescents, and children (6 years old and above) 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.
- Pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with HAE.

Description

ViroPharma Study 0624-401 (Shire Study SHP616-401) was an observational (non-interventional) registry-study conducted to characterize the safety and use of CINRYZE in routine clinical practice in patients with HAE who received CINRYZE for prevention and/or treatment of angioedema attacks.

Methods

Objective(s)

- To characterize the safety and use of CINRYZE in routine clinical practice when administered for routine prevention of angioedema attacks, pre-procedure prevention of angioedema attacks, and/or treatment of angioedema attacks.
- To monitor severe attacks and laryngeal attacks, as well as cases in which treatment with CINRYZE is initiated more than 4 hours after onset of an attack.

The overall objective of the IOS registry is to collect data for analysis and reporting of safety as well as clinical outcome assessments (biological and patient-, clinician-, or observer-reported outcomes)

that will increase the understanding of all HAE types, and where applicable, angiotensin-converting enzyme-I-induced angioedema, non-histaminergic idiopathic angioedema, and acquired angioedema.

Registry Study design

Patients with HAE who were receiving CINRYZE for prevention or treatment of angioedema attacks were enrolled and followed for 12 months at principal centers in Europe.

Study population /Sample size

A total of 83 patients between 8 and 72 years old with HAE who were receiving CINRYZE for prevention or treatment of angioedema attacks were enrolled in Study SHP616-401. Of note, only 1 patient was <18 years old which precludes any generalization or interpretation of the results in pediatric patients.

Of the 83 patients enrolled, 75 (90%) patients received at least 1 dose of CINRYZE for prevention or treatment of HAE attacks; 71 (86%) patients completed and 12 (15%) patients discontinued the study. The reasons for study discontinuation were investigator or sponsor discretion (6 patients), lost to follow-up (4 patients), and withdrawal of consent (2 patients).

Treatments

The majority of patients received CINRYZE for routine prevention (90%] patients) or for treatment of acute attacks (81%] patients). Twelve (16%) patients received CINRYZE for pre-procedural prevention.

67 patients received 4911 doses of CINRYZE for routine prevention. The mean (SD) dose administered to these patients was 1015.62 (93.195) U; all but one patients (66) received at least 1 dose of 1000 U.

12 patients received 33 doses of CINRYZE for pre-procedural prevention. The mean (SD) dose administered to these patients was 1104.17 (249.051) U; all patients received at least 1 dose of 1000 U.

59 patients received 1124 doses of CINRYZE for treatment of acute HAE attacks. The mean (SD) dose administered to these patients was 1063.62 (239.104) U; the majority of patients (56) received at least 1 dose of 1000 U.

Regardless of the indication, the majority of patients received CINRYZE at home (63).

Outcomes/endpoints

- Frequency of HAE attacks
- Severity of HAE attacks
- Anatomic location of HAE attacks
- Outcome of severe or laryngeal HAE attacks
- Outcome of HAE attacks for which treatment with CINRYZE was initiated more than 4 hours after onset of the attack.

The safety outcomes of the study were:

- Incidence of nonserious and serious adverse drug reactions (ADRs)
- Incidence of thrombotic/thromboembolic events

- Occurrence of pregnancy with associated follow-up information.

Statistical Methods

All analyses were descriptive. No formal statistical testing and comparisons were performed for this observational study.

Results

Recruitment / Number analysed

The mean (SD) age at enrollment for Study SHP616-401 was 41.4 (14.10) years. The majority of patients were female (68%). The initial indication for CINRYZE therapy at the time of enrollment was routine prevention (70%] patients) and treatment of HAE attacks (30%] patients).

Baseline data

Certain baseline characteristics were recorded only in patients who consented to Amendment 2 of the protocol (22 patients).

The reason for initiating patients on CINRYZE was available for 19 of the 22 patients who consented to Amendment 2 of the protocol; the majority of them (12 patients) were given CINRYZE because of the high frequency of attacks.

Of the treated patients who consented to Amendment 2 of the protocol, 10 patients were administered C1 INH for on-demand treatment, 8 patients were administered C1 INH for prophylaxis treatment, and 3 patients were administered androgens for prophylaxis treatment within the 3 months prior to the start of CINRYZE treatment.

The number of HAE attacks in the 3 months prior to the start of treatment with CINRYZE was available for 16 patients and ranged from 3 to 24 attacks; the average severity of these attacks was moderate or severe.

Efficacy results

Overall, 73 patients received at least 1 dose of CINRYZE and had a total of 1407 HAE attacks during Study SHP616-401. The mean number of HAE attacks per patient was approximately 19 HAE attacks and the median duration of attacks was 2 days. Approximately 88% of patients had at least 1 attack in multiple locations.

A high proportion of patients (89%) had gastrointestinal/abdominal attacks during the study. Extremity attacks and genitourinary attacks were also common during the study (82% and 60% of patients, respectively). Approximately 30% of patients had laryngeal attacks.

The majority of HAE attacks were of mild (34%) and moderate (42%) severity. 23% severe attacks were reported in treated patients with HAE attacks during the study. The majority of patients (71%) had at least 1 severe HAE attack.

Five of the 12 patients who were administered CINRYZE for pre-procedural prevention experienced at least 1 HAE attack within the 72 hours after the procedure.

Of the 75 patients who received CINRYZE during the study, 73 patients had a total of 1407 attacks during the study (no information on attacks was available for 2 patients). The mean (SD) number of

HAE attacks per patient was 19.27 (16.237). The mean duration of the attacks was 2.21 (1.302) days. The majority of attacks lasted 1 day (45%) or 3 days (35%).

The majority of HAE attacks and severe or laryngeal HAE attacks (59% and 57%, respectively) recovered/resolved without sequelae. Of the HAE attacks that were treated more than 4 hours after the onset of attack (12%), the majority (70%) recovered/resolved without sequelae.

Safety results

Risks of particular interest for CINRYZE and other C1 INH products in patients with HAE include hypersensitivity, thrombosis, the risk of transmission of infectious diseases, and the development of anti-C1 INH antibodies.

A total of 75 (90%) patients received at least 1 dose of CINRYZE during Study SHP616-401. The majority of patients received CINRYZE for routine prevention (89% of patients received 4911 doses) or for treatment of acute HAE attacks (78% of patients received 1124 doses) and fewer patients received CINRYZE for pre-procedure prevention (16% of patients received 33 doses). The mean dose of CINRYZE administered during the study was approximately 1000 U for all indications and more than 96% of doses were of 1000 U. Regardless of the indication, the majority of patients received CINRYZE at home.

Overall, CINRYZE was well tolerated in this study. Six (8%) patients had a total of 11 ADRs related to CINRYZE; all of these patients were adults. Two of the 11 ADRs (moderate depression and moderate nausea) led to CINRYZE discontinuation in 2 patients. There were no ADRs leading to death. There were no thrombotic or thromboembolic events reported during the study.

A total of 5 pregnancies were reported in 5 patients during the study. Two patients had complications during the study (aggravation of HAE crises and risk of premature birth/delivery). All the pregnancies resulted in singleton births; 2 were preterm births (<38 weeks) and 3 were term births (38-42 weeks). The health status at birth was available for 3 infants; all of them were alive and healthy at birth. The data obtained from the pregnancies reported during the study indicate no adverse effects of CINRYZE on pregnancy or on the health of the newborn child.

2.3.3. Discussion on clinical aspects

The only paediatric patient in EU (male) was enrolled and discontinued due to loss to follow-up. No single dose for this patient has been documented in the submitted material. In the context of an Article 46 procedure this finding is considered to be unusual.

Participation in the study was voluntary for patients and doctors. Enrollment rate was slow and the study was discontinued prematurely. Therefore, the final sample size was smaller than initially planned (83 patients vs 125 planned patients).

Number of patients who received at least one dose is not consistent and varies between 73 and 75. Standard single dose was 1000 U.

Baseline data are available for a minority of subjects (22), only. Therefore, any clinical evaluation is considered to be highly challenging.

As baseline data are insufficient, recorded numbers cannot be correlated with baseline characteristics of patients.

From a clinical point of view, "*five of the 12 patients who were administered CINRYZE for pre-procedural prevention experienced at least 1 HAE attack within the 72 hours after the procedure*."

Such numbers would presume 42% pre-procedure-prophylaxis failures – which is considered to be remarkable.
Similarly, “the majority of HAE attacks and severe or laryngeal HAE attacks (59% and 57%, respectively) recovered/resolved without sequelae”: If this information holds true, 324 attacks (23% of 1407) resulted in sequelae (what kind?) - which is considered to be remarkable, too.

Furthermore, information of specific interest would have been the outcome, efficacy and safety during pregnancy in the respective 5 women. However, due to the nature of data-collection and truncated information, available data are considered to be not meaningful.

Overall, evaluation of efficacy is further reduced to percentages related to various indicators. Reliable clinical analysis, e.g. regarding treatment, dosage/timing and outcome of laryngeal or other severe attacks is not available.

Presented safety data are considered to be narrow and do not allow further conclusions.

3. Overall conclusion and recommendation

The only paediatric patient (male) was enrolled and discontinued due to loss to follow-up. No single dose for this patient has been documented in the submitted material. No comment on this index-patient has been included in the overview of the current procedure.

Due to slow enrollment, the registry was discontinued prematurely (final sample size 83 vs 125 planned patients).

Baseline data are available for a minority of subjects, only. Therefore, any clinical evaluation would be considered to be highly challenging.

Information of specific interest would have been the outcome, efficacy and safety during pregnancy in the respective 5 women. However, due to truncated information, available data are considered to be not meaningful.

Overall, evaluation of efficacy is further reduced by the nature of data-collection (registry). Reliable clinical analysis, e.g. regarding treatment, dosage/timing and outcome of laryngeal or other severe attacks is therefore not available.

Presented safety data are considered to be narrow and do not allow further conclusions.

☒ Fulfilled

No regulatory action required.