Assessment report

Cinryze

International Nonproprietary Name: C1 inhibitor, human

Procedure No. EMEA/H/C/001207

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

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List of abbreviations

AE	Adverse event
BW	Body weight
C1	Complement component 1
C4	Plasma complement component 4
C1 INH	C1 esterase inhibitor
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
Cmax	Maximum concentration
COMP	Committee for Orphan Medicinal Products
CSR	Clinical study report
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FFP	Fresh frozen plasma
GCP	Good Clinical Practice
HAE	Hereditary Angioedema
ITT	Intent-to-treat (population)
i.v.	Intravenous
MAA	Marketing Authorisation Application
MRP	Mutual Recognition Procedure
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic(s)
RMP	Risk Management Plan
SAE	Serious adverse event
SAS	Statistical analysis system
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
T1/2	Elimination half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to maximum concentration
TTUR	Time to unequivocal relief
U	Units
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ViroPharma SPRL submitted on 15 July 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cinryze, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 April 2008. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

Cinryze, was designated as an orphan medicinal product EU/3/09/668 on 08-10-2009. Cinryze was designated as an orphan medicinal product in the following indication: Treatment of angioedema caused by C1-inhibitor deficiency. The calculated prevalence of this condition was estimated as 2.1 per 10,000 EU population. In connection with the review of the orphan designation criteria by the Committee on Orphan Medicinal Products (COMP) at its meeting of 6-7 April 2011, the Applicant requested the European Commission to remove the product from the Community Register of Orphan Medicinal Products on 7 April 2011.

The applicant ViroPharma SPRL submitted on 19/10/2009 a revised application for Marketing Authorisation to the European Medicines Agency (EMA) for Cinryze, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication treatment and prevention of angioedema attacks in adults, adolescents and children with C1 inhibitor deficiency.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/193/2009

for the following condition(s):

- C1 inhibitor deficiency

on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver and a deferral.

The PIP is not yet completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application contained a critical report addressing the possible similarity with authorised Firazyr.

Market Exclusivity

Not applicable.

Licensing status

At the time of submitting the application for a marketing authorisation, ViroPharma declared not to have any Marketing Authorisation Application for the same product in the EEA (same qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form from applicants belonging to the same mother company or group of companies or which are "licensees"). Section 4.2 application form was left blank.

During the Procedure, the Agency was informed by a third party of the existence of a Manufacturing and Distribution Agreement between Sanquin and ViroPharma. This agreement entered into force on 8 January 2010 and it has become publicly available. According to this agreement, ViroPharma and Sanquin are to be considered as the same applicant/marketing authorisation holder pursuant to Commission Communication 98/C 229/03.

Sanquin holds a Marketing Authorisation for Cetor, a human C1 inhibitor with the same qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form as Cinryze. Cetor is authorised as a medicinal product in The Netherlands since 1997 and subsequently in Belgium, Finland, France, and Luxembourg by Mutual recognition procedure.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Christian Schneider Co-Rapporteur: Ian Hudson

- The first application was received by the EMA on 15 July 2009. Additional supplementary information during validation was received on 23 September 2009, 19 October 2009, 18 December 2009 and 3 March 2010.
- The procedure started on 24 March 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2010.
- During the meeting on 19-22 July 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 September 2010 and 22 September 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 November 2010.

- During the CHMP meeting on 15-18 November 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 January 2011 and 26 January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's written responses to the List of Outstanding Issues to all CHMP members on 31 January 2011.
- During the CHMP meeting on 14-17 February 2011, based on the written responses provided the CHMP agreed that an Oral Explanation was not necessary and adopted a 2nd list of outstanding issues to be addressed by the applicant in writing.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 23 February 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Questions to all CHMP members on 02 March 2011.
- During the meeting on 14-17 March 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion on the benefit/risk balance to Cinryze on 17 March 2011. The applicant provided the letter of undertaking on the post-authorisation commitments on 16 March 2011.
- The CHMP adopted a report on similarity of Cinryze with Firazyr on 22 July 2010.

2. Scientific discussion

2.1. Introduction

Angioedema attacks are the clinical symptom of a rare autosomal dominant disease caused by a deficiency of functional endogenous C1 inhibitor (C1 INH) activity. C1 INH is a serine protease inhibitor and acts as a regulator of the complement and contact pathways by the formation of pathway-specific complexes. Activation of these complexes, e.g. through trauma or serious infection, leads to consumption of C1 INH. C1 INH deficiency may result in a Hereditary Angioedema (HAE) attack. Attacks present as non-itching swellings of the skin or mucosa, which may affect extremities, face, trunk, gastrointestinal tract, genitourinary system, or larynx. Laryngeal swelling can be life-threatening and these attacks account for the mortality risk described for HAE.

Different therapies are available for HAE disease including Fresh Frozen Plasma (FFP), attenuated androgens, antifibrinolytics, the bradykinin B2 receptor antagonist Icatibant, and C1 INH preparations. Attenuated androgens increase hepatic production of C1 INH protein but are associated with safety and tolerability issues. They are not suitable for the treatment of acute attacks and should be avoided in women of child-bearing potential and children. Antifibrinolytic agents inhibit plasminogen activation with consequent "sparing" of C1 INH consumption but are recognized as less effective for the control of HAE than the attenuated androgens. All antifibrinolytics bear the risk of thromboembolic events. The synthetic bradykinin B2 receptor antagonist Icatibant is suitable for treatment of acute attacks, not for prophylactic therapy. It acts by competitive interference at the level of the bradykinin B2 receptor, while C1 INH raises the functional C1 INH level. The mechanisms of action are thus different between Icatibant and C1 INH. C1 INH concentrate products increase serum levels of C1 INH activity and temporarily restore the natural regulation of the contact, complement, and fibrinolytic systems, thereby controlling the swelling or the propensity to swell. A recombinant C1 INH product has recently been granted marketing authorisation in the indication treatment of HAE-attacks. The indication routine prevention of angioedema attacks is not approved within the EU.

Cinryze belongs to human plasma derived C1 INH products. The applicant applied for the following indication:

- Treatment and prevention of angioedema attacks in adults, adolescents and children with C1 inhibitor deficiency.

As a result of evaluation of available data the agreed indication for Cinryze is:

- Treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with hereditary angioedema (HAE).
- Routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.

Marketing authorisation dossier is an application according to Article 8.3 (new active substance) of Directive 2001/83/EC, as amended - complete and independent application.

Cinryze was designated as an orphan medicinal product EU/3/09/668 on 08-10-2009 in the following indication: Treatment of angioedema caused by C1-inhibitor deficiency. The calculated prevalence of this condition was estimated as 2.1 per 10,000 EU population. Following ViroPharma's request, Cinryze was removed from the Community register of orphan medicinal products in April 2011.

2.2. Quality aspects

2.2.1. Introduction

Cinryze is a heat-treated, nanofiltered C1 inhibitor product, purified from human plasma for fractionation. It is presented as lyophilized powder and solvent for solution for injection for the proposed indication. The product is reconstituted with Water for Injections (5 ml) resulting in 100 U/ml C1-inhibitor, with one unit (U) of C1-inhibitor corresponding to the C1-inhibitor activity in one millilitre of normal human plasma. Cinryze is marketed in secondary packaging containing 2 vials of drug product (500 IU) and 2 vials of solvent WFI. A transfer device and administration set are part of the secondary packaging. Accordance of the devices with the Council Directive 93/42/EEC, as well as compatibility of the devices with Cinryze finished product is demonstrated

2.2.2. Active Substance

Manufacture

Starting material

The starting material for the manufacturing process of Cinryze active drug substance is "plasma for fractionation" according to Ph. Eur. monograph 07/2008:0853. Plasma is provided in the Netherlands by Sanquin, and in Belgium by CAF-DCF cvba-scrl (CAF-DCF, a subsidiary of Sanquin) and in Finland by the Finnish Red Cross Blood Service (FRC). Information on the source, collection, separation and control of the human plasma used as the starting material of Cinryze is provided in the relevant Plasma Master Files of Sanquin and CAF-DCF, respectively.

The purified and concentrated C1 INHC1 INH after pasteurization and nanofiltration is considered as the active substance. All other raw materials are of Ph. Eur. quality or they are qualified according to in house specifications.

In 2008 Cinryze was approved by the FDA and is also produced for the US market. Several studies in this dossier were conducted with American plasma, although US plasma is not covered by this licence application.

Manufacture

The manufacture starts from individual donations that are pooled to make a plasma pool for fractionation. The batch formula is specified to indicate the validated number of donations that can be pooled for further processing.

The manufacturing process for the drug substance is described in sufficient detail. The manufacturing process of Cinryze is basically identical to Cetor including an additional nanofiltration step to improve viral safety. With the introduction of the nanofiltration step the addition of HepB-IgG to the CM eluate before pasteurisation was discontinued.

After separation of the cryo-precipitate and adsorption of the Vit K dependent coagulation factors, the cryo- and 4F-depleted plasma serves as intermediate for further purification of the C1 INHC1 INH. The first homogenous pool (cryo-poor plasma) is subject to viral marker testing in compliance with Ph. Eur. requirements of plasma for fractionation. Acceptable limits for total viable counts of PB19 are specified.

The cryo and 4F-depleted plasma is particle-filtered, followed by diafiltration/ultrafiltration to concentrate the solution. The material is loaded on an ion exchange column to capture C1 INHC1 INH.

The eluted material (eluate) is further processed or stored. After pH adjustment of the eluate, the C1 INHC1 INH containing filtrate is collected. Upon dilution with WFI the material is loaded on an ion exchange column via serial filtration units. After washing the column, the eluate is eluted and pH adjusted. The eluate may be processed or stored. The eluate is stabilized with appropriate stabilisers and concentrated. Trisodium citrate and sucrose is added and the solution is heat-treated (pasteurization).

The pasteurized material is diafiltered and concentrated via haemodialysis filter, filtered and stored overnight. Finally the product is serially filtered and nanofiltrated. The nanofiltrate is concentrated via haemodialysis cartridge and is filtered ("C1 INHC1 INH pasteurized filtrate" representing the bulk drug substance). At this step, the product is immediately processed or can be stored for up to two years.

The ion exchange columns are regenerated for repeated use by a validated process, column re-use cycle numbers have been specified.

Process validation

Validation studies were performed on three conformance lots manufactured from American plasma, manufactured according to the manufacturing process for Cinryze as reported in this dossier.

The set of in process controls established -mostly on the column eluates and the nanofiltrate- indicates that the manufacturing process is sufficiently robust to generate a bulk product of acceptable consistent quality. The equipment used in the manufacture of Cinryze has been subject to validation and regular re-validation, and a consistent equipment performance is demonstrated. The re-use of the ion exchange columns runs has been validated. The freeze-drier is fully validated.

During manufacture several intermediates can be combined for further processing without detectable effect on the process or product quality. The entire set of pooling options has been specified.

Impurities

During the manufacturing of C1-inhibitor the coagulation factors are removed by adsorption. Any residual activity was removed during further processing and no activity is detectable in the drug substance pasteurised nanofiltrate. About 20 % of total protein in Cinryze finished product appear to be impurities and a specification limit for newly identified impurities has still to be set (condition). As a consequence, a purity specification for C1 inhibitor protein should be set as well (condition). Validity of test assays for impurites is shown.

Process-related impurities are reduced to very low level and are of no toxicological concern.

Analytical methods

The analytical test methods are compendial methods for which no further information is presented or these are validated in house tests.

Batch analysis

The test parameters on the bulk drug substance meet requirements and are supportive of a bulk substance of consistent quality. Microbial load is measured before the final sterile filtration step, and endotoxin testing is conducted on the pasteurized filtrate (bulk drug substance prior to 1st sterile filtration) in order to assure low bioburden during the manufacture of the bulk drug substance.

Reference Standards or Materials

Sanquin uses an in-house reference standard for determination of the C1-inhibitor activity because no international standard was available at the start of the procedure. The C1 inhibitor reference standard is considered acceptable and sufficiently qualified as an activity standard. A written procedure is in

place explaining how the C1-esterase inhibitor concentrate control has to be prepared, handled and stored. This batch of purified C1 INH is used as an in-house reference control sample. The applicant will fulfil the condition to calibrate an in-house concentrate standard against the WHO 1st International Standard for C1-inhibitor, concentrate NIBSC code: 08/256 not later than Q4 2011. A control sample representative of the commercial Cinryze finished product has to be established in conjunction with the implementation of the WHO 1st International C1 esterase inhibitor concentrate standard. A retest period has to be be defined once the reference material is calibrated against the international standard.

Container/closure

The container used for the storage of the eluates and the Pasteurised filtrate (Drug Substance) is a polyethylene container. Further information regarding the qualification of the plastic material for long-term storage of intermediate, in particular with respect to leachables entering the product is recommended by CHMP.

Stability

The applicant has presented data for three conformance lots of drug substance according to the final manufacturing process stored over 36 months. Stability of the drug substance under these conditions has been demonstrated satisfactorily, however the initial claim is for 24 months and this should remain. Stability data were originally presented for key intermediates.

Sufficient stability data have been presented for cryo- and 4F depleted plasma; eluates (without HepB IgG) manufactured at Sanquin to support the claimed 24 month shelf-life for intermediate eluate

2.2.3. Finished Medicinal Product

Cinryze is supplied as a sterile, pyrogen-free single-use freeze-dried powder. The nominal fill size is 500 U per vial to be reconstituted with 5 ml solvent WFI provided in a separate vial. Each secondary package of Cinryze contains 2 drug product vials of 500 IU and 2 vials of WFI. The freeze-dried powder is white to light blue, yielding a colourless to light blue solution upon reconstitution. The formulation buffer of Cinryze includes only components of non-animal origin, added to achieve isotonic conditions and to stabilize the product during the lyophilisation process.

For marketing, Cinryze is presented as two 500 U vials instead one 1000 U vial. In all clinical studies always 1000 U are administered at a time, requiring prior pooling of two vials. This unnecessarily complicates the reconstitution process and the patient treatment and may increase the risk of microbial contamination during pooling. The applicant proposes to replace the 2 vials of 500 U by 1 vial of 1000 U once the product has received approval.

The transfer and administration devices are in accordance with Council Directive 93/42/EEC, as amended by Directive 2007/47/EC. Compatiblilty of the devices with Cinryze finished product is demonstrated.

The composition of the final product contains trisodium citrate, sodium chloride, L-valine, L-alanine, L-threonine and sucrose.

Cinryze is provided in colourless glass vials (type I glass, Ph.Eur.) of 8 ml. Water for Injections is provided in colourless glass vials (type I glass, Ph.Eur.) of 11 ml. Vials of product and Water for Injections are closed with bromobutyl stoppers (Ph.Eur.) and sealed with aluminium cap.

Manufacture of the product

The finished product is produced from bulk drug substance lots. After a second sterilisation step in a grade A area the solution is filled into vials and immediately loosely stoppered. Next, the content of the vials is frozen, freeze-dried and the vials are closed. The vials are visually inspected, vacuum controlled and subjected to quality control testing. Finally, labelling and packaging is performed.

Process validation

The buffer production and vial depyrogenisation is sufficiently validated, aseptic conditions during the filling process are confirmed by regular media fill runs. Complete validation data for the freeze-drier used in the manufacture of Cinryze are presented to demonstrate that this step is consistent and robust. All excipients used in the preparation of the finished product are stated to be of Ph. Eur. quality.

Product specification

The finished product specifications after reconstitution describe an isotonic product with a pH and osmolality in the physiologic range. Although there is no specific monograph for C1 inhibitor from human plasma, the specifications of critical parameters are in the range of comparable blood products for intravenous administration

The parameters used in the release testing of the finished product are sufficient to ensure a well-controlled drug product, although some limits need to be tightened post-approval. Test methods are mostly compendial and details are provided. Non-compendial methods are described in sufficient detail and are fully validated.

The level of plasma-derived impurities in the final product has mostly been clarified. There are no purity/identity specifications and in some cases these may be required, depending on the levels of impurities present and the implications for product safety. As a consequence, the applicant has to set specifications for the impurities.

To ensure the consistency of the potency and the purity of the finished product, the applicant should fulfill the following conditions:

- to tighten the finished product specifications for C1 inhibitor activity, for specific activity, and for pH. The adjustment should be based on a statistically significant number of historical and commercial Cinryze batches representative of the current manufacturing process. The specifications have to be implemented by Q4 2011.
- to add a release specification to the finished product for purity of C1 inhibitor protein, determined by a validated, quantitative assay. The specification has to be implemented by Q4 2011.
- to add specifications for the recently identified impurities. The new specifications should be implemented in conjunction with the introduction of the 1st I. S. for C1 inhibitor by Q4 2011.

Stability of the product

The proposed shelf life of the drug product is 36 month at 2-25°C. The shelf life claim is based on data from 9 full scale lots. An in-use stability of 24 h at 20°C is supported by data; an in-use shelf life of 3 h at room temperature (15-25°C) is stated in the SPC. Respective studies were conducted in compliance to ICH recommendations and support the shelf life claim.

Adventitious agents

Cinryze (C1-inhibitor) is produced from human source plasma. Three steps of the production process precipitation, pasteurisation and filtration were validated for their virus inactivating/removing capacity including robustness studies. Enveloped viruses are effectively inactivated during precipitation, pasteurisation and the filtration step. In addition, the filtration step is essential for the safety of Cinryze especially with respect to non enveloped viruses, including both Hepatitis A virus (HAV) and Canine Parvovirus (CPV) an animal model virus for human parvovirus B19. HAV and CPV removal capacity was demonstrated during filtration. As expected, HAV was only moderately inactivated during the pasteurisation step. The animal model parvovirus CPV was not inactivated during this step. An effective removal of CPV was observed using precipitation. In summary, the virus safety of Cinryze has been adequately demonstrated.

No animal-derived TSE risk material added at production was identified. Therefore, the TSE safety of Cinryze seems to be adequately demonstrated.

In addition, the production process of Cinryze has been investigated for its capacity to remove prions. According to guideline CPMP/BWP/CPMP/5136/03 investigational study reports for TSE removal steps during the production process of Cinryze have been provided.

Drug Product (WFI)

Potable city water is the source for the production of purified water according monograph 0008 of Ph. Eur. by ion-exchange-based demineralisation. In a distillation process WFI is produced from purified water. Water for Injections in bulk is filled in 11 ml type I glass vials (according Dutch Ph.), closed with a grey bromobutyl rubber stopper (tested acc. Ph. Eur. monograph 3.2.9) and a light blue flip-off cap. The sealed vials are terminally sterilised by autoclaving. The WFI meets the requirements of monograph 0169 of the Ph. Eur. "Sterilised Water for Injections". Recent Certificates of Analysis for 3 lots of WFI have been presented. The WFI is filled as overfills in order to meet the requirements for the extractable volume. The shelf life of WFI is 5 years at 2-8°C. The qualification of the container/closure system for WFI is demonstrated by recent documents to confirm compliance of vials and stoppers to current Ph. Eur. requirements. The proper operation of the sterilisation oven currently in use is confirmed by validation documents

Medical Device

Adequate information regarding transfer devices or administration devices is submitted with the dossier.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, information on, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The different aspects of the chemical, pharmaceutical and biological documentation are in compliance with existing guidelines.

The quality and safety of the plasma as starting material is covered by a certified PMF. The manufacture of the drug substance have been adequately described, controlled and validated. The drug substance has been well characterised with regard to its physicochemical and biological characteristics and appropriate specifications have been set. The manufacturing process of the drug product has been satisfactorily described and validated. The results of tests carried out indicate

satisfactory consistency and uniformity of important quality characteristics. Although the quality of the drug product is controlled by adequate test methods and specifications, the applicant should include additional specifications for purity and for the recently identified impurities and should calibrate in-house reference material against the WHO 1st international standard in order to ensure the continuous consistency of the potency and purity of the product. The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of the product has been demonstrated. Based on the review of the data on quality, the application for Cinryze is approvable.

In order to ensure the continuous consistency of the potency and purity of the finished product, the applicant should fulfill the conditions in section 2.2.3.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical testing strategy for Cinryze took into consideration the applicable guidelines for plasma derived products as well as the data from successive development of C1 INH products.

Cinryze is a further development of the C1 INH product Cetor, which is approved via Mutual Recognition procedure. The Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals CPMP/ICH/302/95, which is applicable to plasma derived products, does not require a conventional non-clinical programme for the investigation of human proteins. Thus, the extent of additional nonclinical studies with Cinryze was limited.

Overall, the non-clinical development program was conducted to establish the safety of Cinryze for short-term use. No additional pharmacodynamic data was generated for this plasma-derived C1 INH. The *in vivo* pharmacokinetics of C1 INH were assessed within the toxicity studies. The nonclinical toxicology programme included one acute and two repeated-dose toxicity studies in rats. Local tolerability was investigated histophathologically within toxicity studies at the site of tail vein administration. Further toxicity studies were performed to address potential reproductive and developmental toxicity: embryo-fetal development and maternal toxicity were studied in dose-range finding and full embryo-fetal development studies in rats. Additionally, results from studies testing the thrombogenic or immunogenic potential were presented, however within these studies predecessor products have been used.

According to the applicant the toxicology studies were GLP compliant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

No specific studies were performed with Cinryze. However, the Applicant summarised the extensive knowledge of the pharmacodynamic properties of other C1 INH preparations, which is also applicable to Cinryze. Therefore lack of such studies is regarded as justified.

C1 INH inhibits the complement system and of the contact system (intrinsic clotting). The effect on the complement system is achieved via binding of C1 INH to C1r and C1s – two of the active subunits of the first component of the complement system. Binding of C1 INH to factor XIIa and to kallikrein leads to the inhibition of the contact system.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were performed, which was regarded acceptable in view of the existing knowledge about C1 INH.

Safety pharmacology programme

No specific safety pharmacology studies were conducted, which was regarded acceptable in view of the existing knowledge about C1 INH.

Studies on thrombogenicity are presented and discussed in the toxicology part.

Pharmacodynamic drug interactions

No specific studies on pharmacodynamic drug interactions were performed, which was regarded acceptable in view of the existing knowledge about C1 INH and the fact that Cinryze is a plasma derived human protein product.

2.3.3. Pharmacokinetics

The *in vivo* pharmacokinetic of C1 INH was assessed as part of the toxicity studies in rats treated with Cinryze at dose levels of 20, 100 and 400 U/kg. The assay of functional C1 INH concentrations was performed using a validated ELISA based on a commercially available C1 INH kit.

Following single-dose IV administration, the exposure as reflected by area under the plasma concentration-time (AUC_{last}) values, increased dose-proportionally. The highest AUC_{last} values were achieved after administration of 400 U/kg, resulting in values of 83452 and 75378 mU·h/mL in males and female rats, respectively. The terminal half-life of C1 INH ranged between 6.5 and 8.5 hours (see Table 1). No major gender-related differences in systemic C1 INH exposure, accumulation, plasma clearance and volume of distribution of C1 INH were noted.

Table 1. Single dose pharmacokinetic of C1 INHC1 INH obtained after bolus injection in Sprague-Dawley rats

Dose (U/kg)	**AUC_{last} (mU·h/mL)**		**$t_{½}$**		**CL (mL/h/kg))**		**Vdss (mL/kg**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
20	4394	3879	7.9	6.5	3.99	4.77	44.5	45.0
100	26478	23950	8.2	8.0	3.28	3.61	38.1	42.1
400	83452	75378	7.9	8.5	4.22	4.58	47.3	53.2

In general, a similar kinetic profile was observed after single and repeated IV administration of Cinryze for 2 weeks (Study No. DD0002). As shown in Table 2, exposure, as reflected by AUC_{last} values generally increased slightly more than dose-proportionally between the lowest and highest dose. Exposure was generally comparable for both sexes.

Table 2. Repeated dose toxicokinetics of C1 INHC1 INH obtained after IV application of Cinryze for 14 days in Sprague-Dawley rats

Dose (U/kg)	AUC_{last} (mU·h/mL)		$t_{½}$		CL (mL/h/kg))		Vdss (mL/kg	
	M	F	M	F	M	F	M	F
Day 1								
20	3491	3869	7.3	7.1	5.15	4.68	53.8	47.2
100	22373	23347	7.8	7.7	3.95	3.80	43.7	40.8
400	84701	81263	7.7	9.4 [a]	4.16	4.21[2]	43.2	50.2
Day 14								
20	4650	2928	8.5	11.3 [a]	4.30	6.83	53.1	107 [a]
100	21739	20701	7.7	6.8	4.60	4.83	50.5	47.4
400	107374	94575	9.0	9.8[a]	3.73	4.23	46.6	53.4 [a]

[a] accurate determination not possible

As an endogenous human plasma protein, C1 INH is not subject to metabolism by Cytochrome P450 isoenzymes, excretion, or pharmacokinetic interactions exhibited by many low molecular weight compounds. No *in vitro* or *in vivo* metabolism or excretion studies were conducted as the expected consequence of metabolism of a glycoprotein is via degradation to small peptides and individual amino acids. No specific studies assessing tissue distribution or protein binding were performed.

2.3.4. Toxicology

Single dose toxicity

The acute toxicity of C1 INH was studied in Sprague-Dawley rats (Study No. DD0004). Animals (4/sex/group) were dosed intravenously with C1 INH via the tail vein at dosages of 20, 100, and 400 U/kg in sterile water to provide a physiologic solution from reconstituted lyophilized product. A control group (4/sex) received isotonic phosphate buffered saline (PBS) via the same route. Animals were frequently observed until 24 hours after dosing.

There were neither clinical signs nor effects on body weight, body weight gain, hematology, or clinical chemistry. No necropsy findings or effects on organ weight were attributed to the administration of C1 INH. The histopathological examination of tissues revealed a number of common background changes in several tissues but these were expected for rats of this age and strain.

Repeat dose toxicity

7 days repeat dose toxicity study

A 7-day repeat dose toxicity study (4 rats/sex/group) was conducted using a control group and only one dose level of 400 U/kg (Study No. DD0004). No effects were observed on body weights, food consumption, hematology, and clinical chemistry. There were no macroscopic findings at necropsy attributed to administration of C1 INH. No histopathological evaluation was performed. The NOEL for

this study was set at 400 U/kg since a maximum tolerated dose (MTD) was not established in this 7-day toxicology evaluation in rats.

14 days repeat dose toxicity study

In a definite repeat dose toxicity study (study no. DD0002) 10 rats/sex/group were dosed once daily for 14 days with 0, 20, 100, or 400 U/kg of C1 INH. Parameters evaluated included clinical signs, mortality, body weight, food consumption, hematology, clinical chemistry, urine analysis, ophthalmoscopy, immune response, organ weight, and anatomic pathology. Satellite animals were incorporated for toxicokinetic evaluation. In addition, blood was drawn for the evaluation of neutralizing antibodies to product and endogenous C1 INH; baseline anti-C1 INH was established prior to dosing and then on Day 14 of dosing.

One vehicle control group male died on Day 9 immediately after dosing; however this was thought to be due to an air bubble present in the syringe and not related to the vehicle control (PBS). No clinical signs were observed during the 14-day dosing period. Several animals showed signs of scabbing, hair loss and/or lesion at the place where the transponder for identification of the animal was implanted, but these signs were attributed to implantation of the transponder and not related to treatment. There was no treatment-related mortality, alterations in body weight gain, food consumption, ophthalmoscopy, or urinalysis.

Hematology parameters (Hb, RBC, HCT, MCH, MCHC, platelets, reticulocytes, neutrophils, eosinophils, basophils, fibrinogen, PT, and APTT) were not influenced by doses up to 400 U/kg following acute or repeated dosing. White blood cell count, particularly lymphocytes and monocytes were statistically increased compared to vehicle control animals at Day 15 in female animals at all doses. This finding was not observed in males and was not dose-dependent.

There were no toxicologically significant changes in any clinical chemistry parameters (including Na, K, Cl, urea, total protein, albumin, globulins, albumin/globulin ratio, ALP, AST, ALT, cholesterol, creatinine, Ca, total bilirubin, inorganic phosphate and triglycerides) following acute or repeat dosing.

A significant increase in relative spleen weight was noted in both sexes at 400 U/kg. A slight increase in relative lung weight was noted at the same dosage. Notable inflammatory changes in the lungs and spleen germinal center hypertrophy were noted at 400 U/kg.

A dose-dependent positive IgG and anti-C1 INH response was observed in most animals. There was a positive trend in anti-C1 INH response as a function of dose. These results were not unexpected based on the species dissimilarity of a human protein administered to a rat.

Although histopathology findings were noted in the lungs and spleen following repeated daily administration of C1 INH in rats for 14 days, these effects were minor and the toxicological significance of these was equivocal, therefore the NOEL was considered to be 400 U/kg.

Genotoxicity

No genotoxicity studies were performed, which was regarded acceptable since plasma derived human proteins are unlikely to interact directly with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies were performed, which was regarded acceptable for plasma derived human protein triggering development of antibodies in animals.

Reproduction Toxicity

In dose-range finding study No. DD0001 rats (6/group) were dosed with 20, 100 or 400 U/kg from Gestation Day (GD) 6 through GD 17 and euthanized on GD 20, no clinical or necropsy findings were attributed to C1 INH. Intergroup differences in body weight gain and food consumption were considered too small to be attributed to treatment and values for pregnancy performance and fetal weights were similar in all groups.

Exposure to C1 INH in pregnant animals (at dose levels of 20, 100 and 400 U/kg) was comparable to that observed in non-pregnant animals (Study No. DD0002).

In study No. DD0003 20 rats/group were dosed with 20, 100, or 400 U/kg from GD 6 until GD 17 and euthanized on GD 20. No clinical observations or necropsy findings were considered to be treatment-related. Mean body weight gains, food consumption, pregnancy performance values were similar in all groups. A slightly lower number of live implants observed at 400 U/kg reflected the lower number of corpora lutea at this level. Marginal differences in mean fetal weight and sex ratio were considered to be incidental and the type and distribution of the fetal abnormalities and variants, including those indicating the state of skeletal ossification, were similar in all groups and did not indicate any effect of treatment.

Under the conditions of this study, 400 U/kg was identified as the NOEL and NOAEL for both maternal and fetal effects.

Toxicokinetic data

Toxicokinetic data has been generated in study DD002 and is summarised above.

Local Tolerance

No special local tolerance studies were conducted, however, local tolerability was evaluated in toxicity studies, which is acceptable and in line with Note for Guidance CPMP/ICH/302/95. Within studies DD0002 and DD0004, vascular effects of Cinryze application were evaluated histophathologically at the site of tail vein administration and revealed no limited tolerability. Some irritant effects have been observed, but can be explained with application of human proteins in rats. Furthermore, clinical data is available and show low incidence of local reactions. No further investigations on local tolerance are deemed necessary.

Other toxicity studies

In-vitro thrombogenicity testing of the Cinryze predecessor C1 INH-HP implicate that activated vitamin K-dependent coagulation factors, which are thought to be responsible for thrombogenic side effects, are not present in C1 INH-HP. Within the in-vivo thrombogenicity testing (Wessler test), using also C1 INH-HP, a thrombogenic threshold was defined at doses greater than 200 U/kg.

An immunotoxicity study was carried out to determine if the pasteurization step (10 h at 60°C) in the manufacture of C1 INH-HP, an earlier generation product of C1 INH, causes the formation of neo-epitopes on the C1 esterase inhibitor protein (Study No. DD0005). Rabbits received intramuscular (IM; 12 weeks) or IV (6 weeks) immunizations with C1 INH-HP, and sera of these rabbits were examined for the presence of antibodies. As expected, rabbits have no natural cross-reacting antibodies that can recognize human C1 INH-HP. In both groups of immunized rabbits, strong anti-C1 INH responses were found at 1 week after a single immunisation. Subsequent detailed analyses comparing nonpasteurized C1 INH intermediate product and pasteurized C1 INH final product were performed using enzyme

linked immunosorbent assay (ELISA), competitive ELISA, crossimmunoelectrophoresis, and double immunodiffusion. These techniques did not detect any antibodies that were specifically directed against pasteurized C1 INH and not to nonpasteurized C1 INH. Therefore there are no indications that the pasteurization step in the manufacture of C1 INH causes formation of neo-epitopes on the C1 INH protein.

2.3.5. Ecotoxicity/environmental risk assessment

The Guideline on the Environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) states that "aminoacids and proteins […] are exempted [*of environmental risk assessment*] because they are unlikely to result in significant risk to the environment", therefore, an environmental risk assessment is not required.

2.3.6. Discussion on non-clinical aspects

Concerning the primary and secondary pharmacodynamics no specific studies were performed with Cinryze, but the applicant refers to extensive knowledge of the pharmacodynamic properties of other C1 INH products. This approach is considered acceptable.

In pharmacokinetic studies, after single dosing exposure, as reflected by AUC_{last} values, increased dose-proportionally between the lowest and the highest dose with exposure in females comparable to or somewhat lower than those in males. Other pharmacokinetic parameters (e.g., t½, Cl, and Vd) were comparable in males and females. The terminal half-life of functional C1 INH ranged between 6.5 and 8.5 hours. In general, a similar kinetic profile was observed after single and repeated IV administration of Cinryze for 2 weeks. AUC_{last} values generally increased slightly more than dose-proportionally between the lowest and highest dose. Exposure was generally comparable for both sexes. The administration of C1 INH was associated with an expected antibody response due to administration of a human protein to rats therefore negating the value of dosing longer than about two weeks.

Overall, the provided PK data are considered sufficient. Though data as obtained within one species only are considered sparse, further animal pharmacokinetic data are not considered necessary for the particular type of product and also in view of the available clinical data.

In general the number and design of toxicology studies are considered acceptable. The omission of a second relevant species has been justified by the Applicant and is based on the fact that pharmacology of the human C1 INH protein is well characterised and clinical experience has been obtained.

Results of single dose and repeat dose toxicity studies in rats revealed no safety signals over the dose range tested. In the repeat dose toxicity study histopathology findings were noted in the lungs and spleen, but as these effects were minor and the toxicological significance was considered equivocal, the NOEL was considered to be 400 U/kg.

C1 INH was tested for reproductive toxicity, local tolerance and thrombogenicity, and was found to be without notable toxicity. Immunotoxicity study revealed no additional immunogenicity as compared to nonpasteurized C1 INH.

The results of toxicity testing revealed no safety signals up to doses corresponding to maximum 28-fold the recommended human dose (which is 1000 IU), based on an average adult body weight of 70 kg. Thus, from the presented data no safety concerns arise against the use of Cinryze in the intended dose range.

2.3.7. Conclusion on the non-clinical aspects

The preclinical testing strategy is regarded as appropriate in view of the facts that the product is a preparation of a human protein, clinical experience has already been obtained and data for other C1 INH products is available. The applicable regulatory guidelines were taken into consideration adequately. From the presented data no safety concerns arise against the use in the intended dose range. The presented preclinical data is considered appropriate and sufficient. The wording of the SmPC reflecting non-clinical aspects is considered appropriate.

2.4. Clinical aspects

2.4.1. Introduction

Clinical development programme of Cinryze consists of:

- Open-label PK study and a supportive PK study;
- double blind placebo controlled pivotal study and an open label study for treatment of acute HAE attacks;
- double blind placebo controlled pivotal study and an open label study for long-term prophylaxis of HAE attacks.

An approved Paediatric Investigation plan is ongoing for Cinryze and compliance was checked during the validation procedure. The PIP foresees that an open-label, dose-response study to evaluate the response and pharmacokinetics/pharmacodynamics of C1 inhibitor for treatment of acute attacks in children less than 12 years of age with hereditary angioedema will be completed by end of June 2013 (last patient, last visit).

CHMP has been informed by the Applicant that Study VP 0624-400, a dose escalating study in the prophylactic therapy with Cinryze, is currently ongoing.

No formal Scientific Advice/Protocol Assistance was given by the CHMP or any member state.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3. Tabular Listing of Clinical Studies

Study Number	**Study Design**	**Study Objective(s)**	**Test Product(s); Dosage Regimen; Duration of Treatment**	**Number of subjects; population**
KB2003.01A	Randomized, double blind, controlled cross-over	Compare PK, biological activity and safety of C1-esteraseremmer-N with the C1-inhibitor product Cetor®	Randomized Study Drug: C1-esteraseremmer-N or Cetor® 1000, 1500 or 2000 U	14 subjects with HAE without signs of attack

LEVP 2006-5	Phase 1, randomized, parallel-group, open-label	PK of one or two doses	Single Dose: Cinryze 1000 U Two Doses: Cinryze 1000 U followed by a second 1000 U dose 60 min later	27 subjects with HAE (Single Dose: 13, Two Doses: 14)
LEVP 2005-1 /Part A	Phase 3, randomized, double-blind, placebo-controlled	Safety and efficacy for the treatment of acute HAE attacks	Randomized Study Drug: Initial dose of Cinryze 1000 U or placebo; if no response at 60 min, second dose (Cinryze 1000 U or placebo) Rescue Cinryze: If airway compromise after randomized treatment OR no symptom relief within 4 h of initial dose, Cinryze 1000 U; if necessary at 60 min, second 1000 U dose Open-label Cinryze: Pre-surgery: Cinryze 1000 U Laryngeal angioedema: Cinryze 1000 U; if necessary at 60 min, second 1000 U dose	83 subjects with HAE 71 randomized (36 Cinryze, 35 placebo); 12 open-label only
LEVP 2005-1 /Part B	Phase 3, randomized, double-blind, placebo-controlled, crossover	Safety and efficacy for the prevention of HAE attacks	Randomized Study Drug: Cinryze/Placebo: Cinryze 1000 U 2x/week for 12 weeks, followed by placebo 2x/week for 12 weeks. Placebo/Cinryze: placebo 2x/week for 12 weeks, followed by Cinryze 1000 U 2x/week for 12 weeks Open-label Cinryze: Pre-surgery: Cinryze 1000 U Laryngeal angioedema or investigator's discretion: Cinryze 1000 U; if necessary at 60 min, second 1000 U dose	26 subjects with HAE 25 randomized (Cinryze/Placebo: 12, Placebo/Cinryze: 12, 1 randomized not treated); 1 open-label only
LEVP 2006-1	Open-label	Safety and efficacy of repeat use for the treatment of acute HAE attacks	Treatment: Cinryze 1000 U; if no response at 60 min, second 1000 U dose	113 subjects with HAE

			Short-term Prophylaxis: Pre-surgical/dental procedure: Cinryze 1000 U	
LEVP 2006-4	Open-label	Safety and efficacy for the prevention of HAE attacks	Prophylaxis: Cinryze 1000 U every 3-7 days for the duration of the study Treatment: Cinryze 1000 U; if necessary at 60 min, second 1000 U dose	146 subjects with HAE

2.4.2. Pharmacokinetics

The pharmacokinetics of antigenic and functional C1 INH were primarily evaluated from results of study LEVP2006-5, a randomized open-label, parallel group clinical pharmacology study designed to evaluate PK and PD in non-symptomatic HAE subjects given one or two 1000 U doses of Cinryze. Study included subjects 18 years or older who were currently or previously enrolled in LEVP 2005-1 Subjects in single dose group received a single dose of 1000 U, while subjects in double dose group received a first dose of 1000 U followed by a second dose of 1000 U after 1 hour. Serial blood samples, taken over a 7-day period, were assayed for antigenic and functional C1 INHC1 INH and complement C4.

Antigenic C1 INH and Complement C4 levels were determined by validated immunoturbidimetric assays. Quantification of functional C1 INH protein was performed with a validated commercially available enzyme inhibition immunoassay.

For the antigenic C1 INH the applicant's assays were presented as mg/dl and the defined normal range was 21-39 mg/dl (1.23 U/L - 2.29 U/L according to the conversion factor provided by the Applicant). The assay used for functional C1 INH states that the reference "normal range" is >68% (corresponding to 0.68 U/ml according to the conversion factor provided by the Applicant).

A total of 27 subjects were randomized and treated. Of these, 13 received a single dose (1000 U dose) and 14 received a single 1000 U dose followed by a second dose of 1000 U administered 1 hour after completion of the first dose. Baseline concentrations of antigenic and functional C1 INHC1 INH were approximately 0.8 and 0.3 U/mL, respectively. These low baseline concentrations (<1 U/mL) confirmed that these HAE subjects were deficient in C1 INHC1 INH levels.

The mean pharmacokinetic parameters for antigenic and functional C1 INH obtained in this study are displayed in the following tables.

Table 4. Mean (+/-SD) pharmacokinetic parameters for antigenic C1 INH in HAE subjects following administration of Cinryze in Study LEVP 2006-5

Parameter	Single Dose[a]	Double Dose[b]
$C_{baseline}$ (U/mL)	0.86 ± 1.45 (n=13)	0.76 ± 0.71 (n=14)
C_{max} (U/mL)	1.48 ± 1.44 (n=13)	1.70 ± 0.80 (n=14)
Baseline-corrected C_{max} (U/mL)	0.62 ± 0.40 (n=13)	0.95 ± 0.30 (n=14)
t_{max} (h) [median (range)]	[1.2 (0.1 – 52.2)] (n=13)	[1.5 (1.0 – 4.2)] (n=14)
AUC_{0-t} (U·h/mL)	183 ± 254 (n=13)	174 ± 113 (n=14)
Baseline-corrected AUC_{0-t} (U·h/mL)	35.8 ± 35.3 (n=13)	53.1 ± 28.5 (n=14)
Cl (mL/min)	0.65 ± 0.60 (n=8)	0.70 ± 0.36 (n=11)
$t_{1/2}$ (h)	45 ± 12 (n=8)	47 ± 22 (n=11)

Data source: Section 2.7.2.2.3.2.1, Table 2 of Module 2.7.2
n=number of subjects evaluated; $C_{baseline}$=concentration at baseline; t_{max}=time to maximum observed concentration; Cl=clearance; $t_{1/2}$=terminal half-life
Single dose = 1000 U
Double dose = 1000 U followed by a second 1000 U dose 60 minutes later

Table 5. Mean (+/-SD) pharmacokinetic parameters for functional C1 INH in HAE subjects following administration of Cinryze in Study LEVP 2006-5

Parameter	Single Dose[a]	Double Dose[b]
$C_{baseline}$ (U/mL)	0.31 ± 0.20 (n=12)	0.33 ± 0.20 (n=12)
C_{max} (U/mL)	0.68 ± 0.08 (n=12)	0.85 ± 0.12 (n=13)
Baseline-corrected C_{max} (U/mL)	0.37 ± 0.15 (n=12)	0.51 ± 0.19 (n=12)
t_{max} (h) [median (range)]	[1.2 (0.3 – 26.0)] (n=12)	[2.2 (1.0 – 7.5)] (n=13)
AUC_{0-t} (U·h/mL)	74.5 ± 30.3 (n=12)	95.9 ± 19.6 (n=13)
Baseline-corrected AUC_{0-t} (U·h/mL)	24.5 ± 19.1 (n=12)	39.1 ± 20.0 (n=12)
Cl (mL/min)	0.85 ± 1.07 (n=7)	1.17 ± 0.78 (n=9)
$t_{1/2}$ (h)	56 ± 35 (n=7)	62 ± 38 (n=9)

According to the baseline levels of antigenic C1 INH, all subjects were below the "normal range". Following administration of C1 INH, the mean Cmax level was within the "normal range" with a very wide SD (1.44 U/ml) meaning that many subjects did not reach the normal range even at Cmax post-infusion.

Cmax for functional C1 INH together with the antigenic C1 INH data suggest that the single 1000U dose may be on the borderline for achieving levels within the defined normal range.

Additional PK data were obtained in placebo-controlled studies LEVP 2005-1/A and LEVP 2005-1/B; the data is presented in the below tables. For details on the study design see section "Clinical efficacy".

Table 6. Mean (SD) concentrations of functional C1 INH protein in HAE subjects in Study LEVP 2005-1/Part A Efficacy Dataset

Time Point	Cinryze (N=35)			Placebo (N=33)	
	Observed Value (%)	Change from Baseline[a]	p-value[c]	Observed Value (%)	Change from Baseline[a]
Pre-infusion	35.6 (22.62), n=34	-	-	33.7 (29.04), n=31	-
1 h Post-inf	67. 7 (21.94), n=35	31.5 (23.94), n=35	<0.0001	28.8 (24.27) n=32	-6.4 (23.73), n=32
2 h[b] Post-inf	81.1 (15.75), n=23	45.6 (23.70), n=23	<0.0001	38.4 (24.94), n=26	1.0 (12.43), n=26
4 h Post-inf	73.9 (23.60), n=28	34.5 (28.22), n=28	<0.0001	35.8 (24.75), n=25	4.3 (26.02), n=25
12 h Post-inf	71.7 (15.53), n=19	34.8 (17.24), n=19	0.0022	34.4 (19.58), n=14	5.1 (32.09), n=14
3 mos Post-inf	34.5 (24.84), n=17	-8.1 (29.11), n=17	0.8803	25.7 (24.37), n=10	-7.3 (25.83), n=10

Data Source: Table 14.12, Section 14 of LEVP 2005-1/A CSR (see Module 5.3.5.1)

[a] Baseline is defined as the last available non-missing record prior to infusion

[b] Only subjects who received a second infusion of study drug have a 2 h post-infusion sample.

[c] p-values vs. change from baseline in placebo treatment group; Wilcoxon rank sum test.

Table 7. Mean concentrations of functional C1 INH protein in HAE subjects in Study LEVP 2005-1/Part B Efficacy Dataset

Time Point	Cinryze (N=22)			Placebo (N=22)	
	Observed Value (mg/dL)	Change from Baseline[a]	p-value[b]	Observed Value (mg/dL)	Change from Baseline[a]
Visit 1					
Pre-inf	33.9 (17.21), n=20	-	-	31.7 (21.54), n=22	-
1 h Post-inf	62.6 (20.89), n=22	32.0 (18.95), n=20	<0.0001	29.3 (24.42), n=22	-2.4 (9.41), n=22
Visit 8					
Pre-inf	40.9 (25.49), n=21	5.0 (23.92), n=20	0.6542	36.4 (23.40), n=22	4.7 (25.59), n=22
1 h Post-inf	71.2 (12.56), n=21	36.6 (17.62), n=20	<0.0001	37.0 (22.24), n=22	5.3 (26.16), n=22
Visit 16					
Pre-inf	39.2 (21.57), n=20	6.6 (18.74), n=19	0.6028	36.4 (24.06), n=20	3.7 (23.78), n=20
1 h Post-inf	65.4(12.42), n=20	32.1 (19.08), n=19	<0.0001	36.8 (22.05), n=20	5.4 (15.74), n=20
Visit 24					
Pre-inf	38.2 (22.46), n=21	1.5 (19.04), n=19	0.7156	31.6 (22.18), n=21	-0.1 (27.96), n=21
1 h Post-inf	69.0 (12.79), n=21	33.9 (21.07), n=19	0.0002	33.9 (21.16), n=19	0.8 (23.92), n=19

Data Source: Table 14.11, Section 14 of LEVP 2005-1/B CSR (see Module 5.3.5.1)

[a] Baseline is defined as the last available non-missing record prior to infusion

[b] p-values vs. change from baseline in placebo treatment group; Wilcoxon rank sum test.

The applicant was requested by CHMP to provide PK data analysed also by U/Kg dose received for both antigenic C1 INH and functional C1 INH.

For study LEVP 2006-5 body weight was not collected, which precluded formal evaluation of PK parameters on a U/kg basis. However, body weight data were available for 7 patients who had also participated in study LEVP 2005-1/A, which allowed such calculation. Please see below table for the results.

Table 8. Baseline-corrected Cmax, AUC0-t, and AUC0-inf Parameters Normalized by Dose and Body Weight for Selected Subjects in Study LEVP 2006-5

Subject	Dose (U/kg)	C1 INH Antigen			Functional C1 INH		
		C_{max} (U/mL)	AUC_{0-t} (U·h/mL)	AUC_{0-inf} (U·h/mL)	C_{max} (U/mL)	AUC_{0-t} (U·h/mL)	AUC_{0-inf} (U·h/mL)
01-004	12.03	0.0071	0.33	0.42	0.0028	0.06	0.06
01-005	36.23	0.0096	0.38	0.43	0.0082	0.61	NE
05-001	10.22	0.0174	1.41	NE	0.0039	0.39	NE
07-003	18.52	0.0030	0.20	0.22	NE	NE	NE
07-012	10.71	0.0038	0.05	0.09	0.0030	0.06	NE
13-003	26.25	0.0085	0.46	0.66	0.0044	0.33	0.52
13-004	9.67	0.0034	0.11	0.25	NE	NE	NE

Values represent baseline-corrected C_{max}, AUC_{0-t}, and AUC_{0-inf} parameters normalized by dose (1000 U) and body weight.
NE = not estimable.

No correlation was found between the dose normalized by body weight and the observed increase from baseline with respect to Cmax for C1 INH antigen or functional C1 INH activity.

Additional PK data adjusted by body weight was derived from main pivotal study for treatment of acute attacks (LEVP 2005-1/B), where no correlation was found between the dose normalized by body weight and the pre-to post-infusion changes of C1 INH antigen or functional C1 INH activity.

Dose proportionality and time dependencies

In study LEVP2006-5 2-fold increase in dose led to increase in maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC), but not in a dose proportional manner. The reason for this lower-than-expected PK response is unknown.

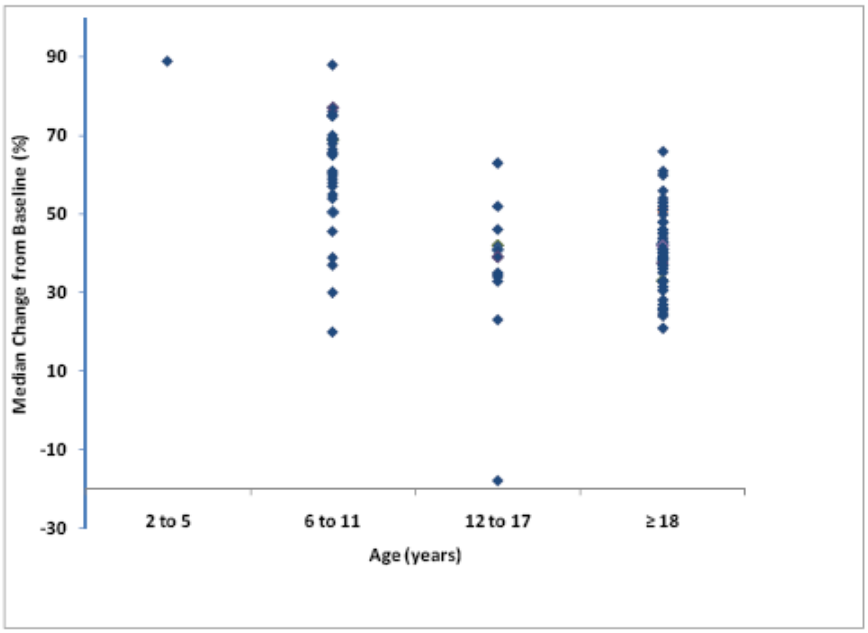
Increases in functional C1 INH activity were independent of duration of study participation indicating consistent pharmacokinetics over repeated Cinryze administrations.

Special populations

Supportive PK data were provided from open-label studies LEVP 2006-1 and LEVP 2006-4, which allowed for inclusion of children above the age of 1 year.

In general, children and adults received a fixed dose of 1000 U of Cinryze. The age group of the 2-5 year old was only represented by in total 3 subjects. It is of note that the single child in this age group in study LEVP 2006-1 (2 years old) as well as one 3 year-old in LEVP 2006-4 received only 500 Units, but presented very high functional responses.

Figure 1. Summary of Median Change in Functional C1 INH Values from Pre- to Post-Infusion by Age in Study LEVP 2006-1



Maximal levels could even be higher, since tmax has not been determined for children. Based on these results, dose recommendations for the use in children cannot be established. It is noted that the dose for children initially proposed by the Applicant (1000 U plus optional second 1000 U) could especially for small children be too high and that safety risks e.g. thrombogenicity cannot be excluded.

Pharmacokinetic interaction studies

Pharmacokinetic interaction studies have not been performed, which was regarded acceptable in view of the existing knowledge about C1 INH and the fact that Cinryze is a plasma derived human protein product.

Pharmacokinetics using human biomaterials

Pharmacokinetic studies using human biomaterials have not been performed , which was regarded acceptable in view of the existing knowledge about C1 INH.

2.4.3. Pharmacodynamics

Since C1 INH is an endogenous protein, the pharmacodynamics and mechanism of action are well known and no pharmacodynamic studies were performed in healthy subjects.

Mechanism of action

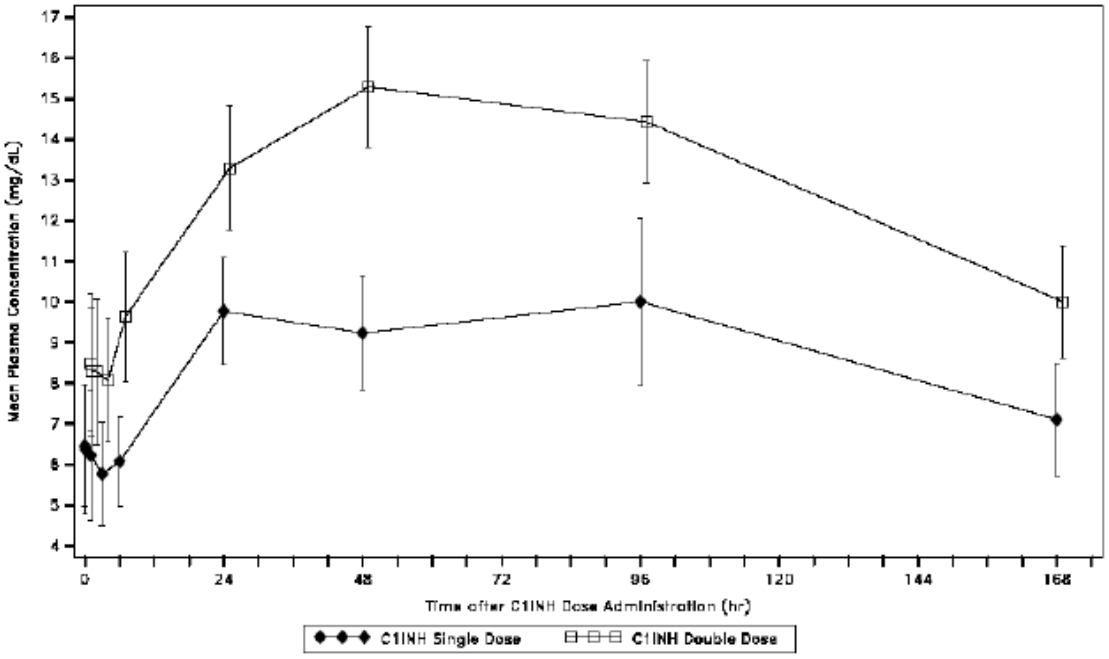
The primary function of C1 INH is to regulate activation of the complement and contact pathways. This is accomplished through the formation of pathway-specific complexes that result in inactivation of the target protease and consumption of C1 INH. C1 inhibitor inhibits the complement system by binding C1r and C1s, two of the active enzyme subunits of the first component of the complement system (C1) in the classical pathway. The primary substrate of the activated C1 enzyme is C4; uninhibited C1 results in diminished C4 levels. An increase in C4 levels is therefore a surrogate measure of the biological effect of Cinryze.

C1 inhibitor regulates the contact system and the intrinsic coagulation (kallikrein-kinin) pathway by binding to and inactivating kallikrein and factor XIIa. Because these pathways are part of enzyme amplification cascades, without C1 INH, spontaneous or trigger-induced activation of these pathways can lead to unopposed activation and swelling.

Primary and Secondary pharmacology

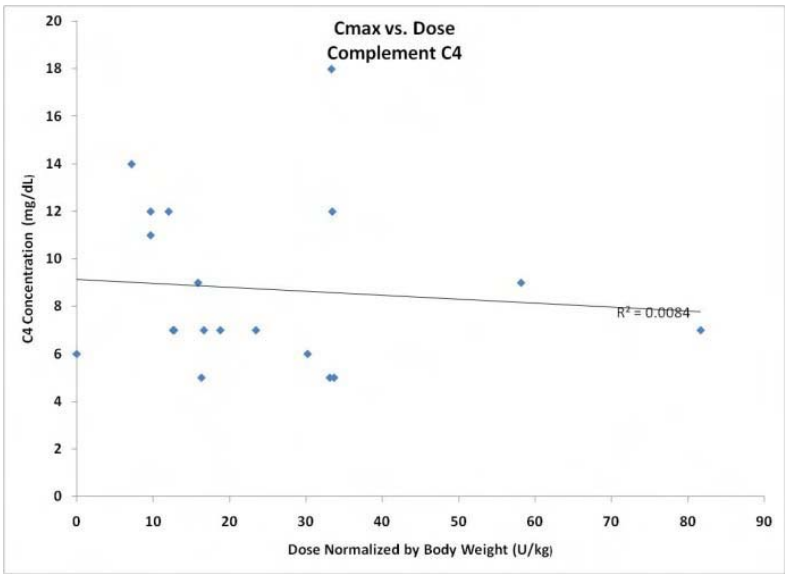
The pharmacodynamic effect of Cinryze on C4 levels was primarily evaluated in Study LEVP 2006-5.

Figure 2. Mean Concentrations of Complement C4 in HAE Subjects Following Administration of Cinryze in Study LEVP 2006-5



The applicant was requested by CHMP to provide PD data analysed also by U/Kg dose received. Such data were available for 7 patients (see PK section).

Figure 3. Plots of Cmax for C4 versus Dose Normalized by Body Weight for Subjects in Study LEVP 2005-1/A



Administration of 1000 U or 2000 U of Cinryze to non-symptomatic HAE subjects resulted in increase in complement C4 levels, which for most subjects were the highest one to two days post-infusion. This increase was not dose-proportional but in similar relation to the dose as observed with functional C1 INH levels.

No correlation was found between the dose normalized by body weight and obtained complement C4 levels.

Additional PD data was derived from Study LEVP 2005-1/A. Pre-infusion, the mean values of C4 antigenic activity were below normal and similar in both the Cinryze group (8.1 mg/dL) and the placebo group (6.7 mg/dL). There was a statistically significant (p=0.0017) difference in the changes in mean values from baseline between the treatment groups at 12 hours, demonstrating the association of Cinryze therapy with an increase in C4 activity (Cinryze +2.9 mg/dL vs. placebo +0.1 mg/dL).

The normal range for C4 (using the immunoturbidimetric assay) is 16-70mg/dl and was not achieved with a single dose in either study.

2.4.4. Discussion on clinical pharmacology

The PK data provided show that the half-life (56 ± 35 hrs for C1 INHC1 INH function) and volume of distribution (2.9 ± 3.12L) are as expected for a C1 INH. Although the half-life of Cinryze was shown to be relatively long, twice weekly administrations of 1000 U did not significantly increase the steady state (pre-infusion) levels of C1 INH, thus giving no evidence of accumulation. C_{max} and AUC increased from single to double dose, but not in a dose-proportional way. Placebo-controlled studies LEVP 2005-1/A and LEVP 2005-1/B revealed statistically significant increases from baseline in antigenic and functional C1 INH levels in the Cinryze treatment group compared to the placebo group.

PK data from the pivotal trial LEVP 2005-1/Part A show that for the patients (n=35) who were tested 1 hour after 1000 U the C1 INHC1 INH function was 67.7% (SD 21.9) meaning that many subjects do not reach the normal C1 INH level of >68%. The CHMP questioned the proposed fixed dose regardless of weight in view of the lack of dose finding studies, the low achieved levels of antigenic and functional C1 INH, and PD parameter C4 after dosing with 1000 U . The Applicant argued that levels of C1 INH have not been shown to be associated with the severity of the disease, although all patients have low C1 INH or a nonfunctioning protein (Frank et al., 1976). Patients who have a mildly decreased C1 INH level may have severe clinical symptoms and patients who have severely depressed levels may have mild manifestations of the disease. The reasons for this are unclear but are likely to be multifactorial and not simply related to plasma levels. Keleman et al (Clinical Immunology 2010; 134; 354-358) have recently demonstrated that baseline levels of functional C1 INH correlate with disease severity scores in HAE. However, there is a high variability of C1 INH functional levels within all severity groups – mean C1 INH functional levels as low as 47% of normal were associated with no symptoms and mean levels of 39% with only minimal symptoms. This supports the position that disease management does not require an increase of C1 INH functional levels into normal range (>68%). Therefore it was concluded that there is no convincing data that C1 INH levels need to be increased to "normal range" in order to effectively prevent or treat acute HAE attacks. The CHMP agreed with this position and accepted a fixed dose instead of a dose adjusted to body weight.

The lack of adequate PK data in children for the age group of 12 years and younger does not allow for dose recommendations in this population. The CHMP therefore requested the restriction of the indication to the use in adults and adolescents. It was noted that the Applicant is conducting a paediatric trial (Study No. 0624-203) to evaluate the dose response and PK/PD of Cinryze for the

treatment of acute HAE attacks and determine the safety and tolerability following IV administration of Cinryze in children less than 12 years of age. Results from this study are requested to be reported.

2.4.5. Conclusions on clinical pharmacology

The PK and PD data demonstrated that Cinryze has the expected effect of raising levels C1 INHC1 INH and C4. It is noted that in the study many subjects did not achieve a level of C1 INH (antigenic or functional) above the lower limit of normal. The consideration whether full physiologic levels are actually necessary to stop a HAE attack was discussed. In a subset of patients for whom PK data and weight were available, no correlation was found between the administered dose per kg bodyweight and the achieved changes to baseline or the maximal levels of C1 INH antigen, functional C1 INH or C4. It is therefore concluded that it is acceptable to use a fixed dose as proposed by the Applicant. The available PK data is however supportive for granting Marketing Authorisation only in age groups of adults and adolescents.

2.5. Clinical efficacy

2.5.1. Dose response studies

No formal dose response studies have been performed, which was justified by the Applicant based on available clinical experience with other C1 INH products. Please refer to discussions on clinical pharmacology and clinical efficacy for more information about the choice of dosage.

2.5.2. Main studies

Study LEVP 2005-1/Part A

Methods

Study LEVP 2005-1/Part A was a Phase 3, randomized, double-blind, placebo-controlled, multicentre study to evaluate the safety and efficacy of Cinryze for the treatment of acute HAE attacks.

Study Participants

Subjects could be eligible, if they had a confirmed diagnosis of HAE with evidence of a low C4 level and either a low C1 INHC1 INH antigenic level, low C1 INHC1 INH functional level, or a known HAE causing C1 INHC1 INH mutation and age ≥ 6 years. The exclusion criteria included: low C1q level; history of a B-cell malignancy; presence of an anti-C1 INHC1 INH antibody; history of allergic reaction to C1 INHC1 INH or other blood/plasma products; pregnancy: narcotic addiction, narcotic pain medication within 7 days prior to the attack. Within four hours of experiencing an "defining symptom" – acute moderate or severe HAE attack of the abdomen (with abdominal pain), face (without airway involvement), or external genitalia (with swelling of scrotum or vulva) the subject was to be further evaluated for eligibility to be randomized.

Treatments

Subjects were treated for a single HAE attack by intravenous infusion over 10 minutes with blinded study agent, either 1000 U Cinryze (n=36) or placebo (n=35). A second dose of the same treatment (i.e. either 1000 U Cinryze or placebo) was to be provided at 60 minutes if the initial treatment had no effect. Rescue treatment with open label Cinryze could be given 4 hours after initial treatment if subjects still had not reported onset of significant relief.

Subjects were not to have received narcotic pain medication within 7 days prior to the attack.

Objectives

To evaluate safety and efficacy of Cinryze for the treatment of acute HAE attacks.

Outcomes/endpoints

After infusion with study drug, subjects evaluated the severity of their "defining symptom" every 15 minutes for 4 hours or until substantial relief of symptoms occurred by using the following scale: "Absent now and before", "Absent now but present before", "Present, symptoms new", "Present, symptoms worse or the same" and "Present, symptoms better". These assessments were used to identify the time to the beginning of unequivocal relief (primary efficacy endpoint), defined as the first of 3 consecutive reports of either "present, symptoms better" or "absent now but present before" or "absent now and before" verifying substantial relief.

Secondary efficacy endpoints included:

- percentage of subjects with beginning of unequivocal relief of the defining symptom within 4 hours following initial randomized treatment;
- time to complete resolution of the attack (recorded at the 3-day telephone follow-up);
- effects of treatment on C1 INH and complement C4 levels (see PK part of AR).

Additional analyses were performed on:

- rating of symptom pain intensity using a visual analog scale (VAS);
- hospitalization following treatment with Cinryze for laryngeal attacks;
- use of rescue treatment (i.e., Cinryze and narcotics).

Sample size

Based on an estimate of 0.83 hours for the primary efficacy endpoint, 34 subjects per treatment group were required to give a total of 65 observed events (providing 80% power at the 5% level of significance (2-sided test) to detect a 50% reduction in primary efficacy endpoint).

Randomisation

Patients were randomized in a 1:1 ratio to receive either Cinryze or placebo. Randomisation was stratified by study centre.

Blinding (masking)

The study was blinded to the investigators and the subjects. At each centre there was an unblinded study pharmacist.

Statistical methods

Time-to-event data were compared between treatment groups by means of a Proportional Hazards Regression (PHR) model including factors 'treatment' and 'centre'. Treatment effects were described by means of the hazard ratio, including the corresponding 95%-confidence interval. Median time to event and its 95% confidence interval were calculated by means of the Kaplan-Meier estimator. The Kaplan-

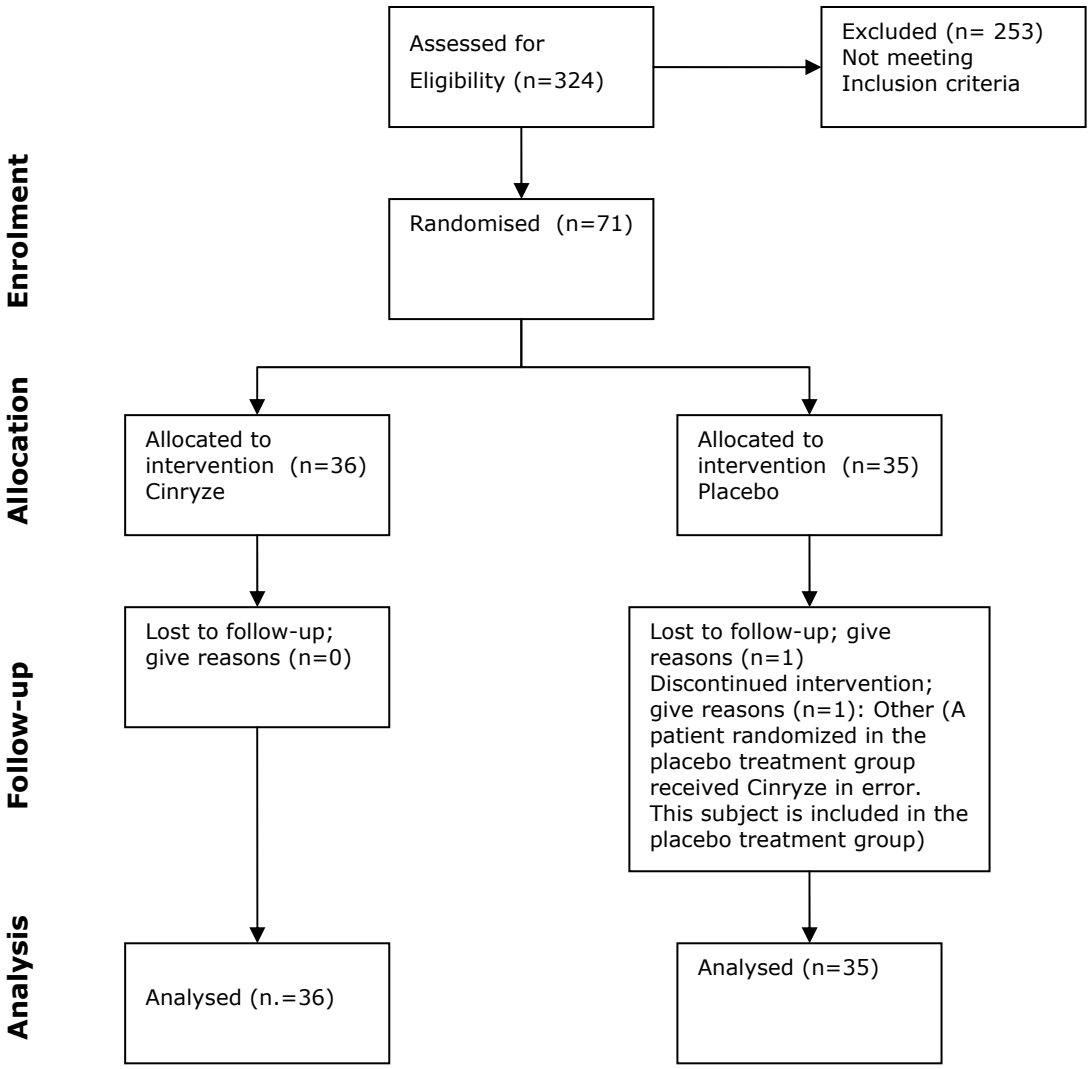
Meier estimates were displayed graphically. Continuous or ordinal variables were compared between treatments either using an analysis of variance (ANOVA) including treatment and centre or a Wilcoxon-rank sum test. The Cochran-Mantel-Haenszel (CMH) test, stratified by centre was used to compare treatment groups for categorical variables.

In addition to the ITT dataset an Efficacy dataset was defined excluding three patients who were retrospectively assessed as not having had a "true" HAE attack. Primary endpoint was analysed in both ITT and Efficacy datasets, while most secondary analyses were not performed on the ITT dataset but on the 'Efficacy dataset'.

For primary efficacy endpoint analysis, subjects who withdrew from the study or received rescue treatment were censored at the time of withdrawal/rescue treatment, and subjects who did not achieve unequivocal relief within 4 hours were censored at 4 hours.

Results

Participant flow



Recruitment

Patients were treated at 21 centres in the US. The first subject was enrolled into the study on 14 March 2005, the last patient completed the study on 13 April 2007.

Conduct of the study

There were 3 amendments to the initial protocol, including change of randomized subjects from 62 to 70, and change of time-point for rescue with open-label Cinryze and symptom assessment from 8 to 4 hours.

Baseline data

With respect to age, gender and height, both treatment groups were balanced. With respect to weight subjects randomized to Cinryze were slightly heavier than those randomised to placebo (median weights: Cinryze – 78.5 kg, Placebo – 69.6 kg).

Table 9. Demographic characteristics (ITT Dataset Study LEVP 2005-1/Part A)

Variable	Statistic	Cinryze (N=36)	Placebo (N=35)	Open-label C1INH-nf [1] (N=12)
Age (years)	n	36	35	12
	Mean	36.8	37.0	36.3
	SD	17.68	13.76	19.42
	Median	36.5	38.0	36.5
	Range	6 - 75	9 - 64	9-73
Gender, n (%)	Male	9 (25.0)	7 (20.0)	6 (50.0)
	Female	27 (75.0)	28 (80.0)	6 (50.0)
Ethnic Origin, n (%)	White/Caucasian	34 (94.4)	32 (91.4)	9 (75.0)
	Black/African American	1 (2.8)	1 (2.9)	2 (16.7)
	Hispanic/Latino	1 (2.8)	2 (5.7)	1 (8.3)
	Asian	0	0	0
	American Indian or Alaska Native	0	0	0
	Native Hawaiian or Pacific Islander	0	0	0
	Other	0	0	0
Weight (kg)	n	35	35	12
	Mean	80.49	77.63	78.53
	SD	27.995	22.103	30.323
	Median	78.50	69.60	71.35
	Range	24.5 - 149.6	52.6 - 149.2	34.9 - 158.8
Height (cm)	n	35	35	12
	Mean	163.29	167.67	166.83
	SD	14.009	10.360	16.692
	Median	166.10	166.40	168.00
	Range	116.1 - 177.8	147.3 - 200.7	128.3 - 190.5

Data Source: Section 14, Table 14.2.2 and Appendix 16, Listing 16.2.4

With respect to symptom severity at baseline, 'severe' HAE attacks were more often reported for patients randomized to placebo.

Table 10. Defining Symptoms - VAS and Severity Prior to Treatment (Efficacy Dataset Study LEVP 2005-1/A)

Parameter	Cinryze (N=35)	Placebo (N=33)
Defining Symptom, N (%)		
Gastrointestinal (abdominal pain)	24 (68.6%)	26 (78.8%)
Genitourinary	7 (20.0%)	2 (6.1%)
Facial	4 (11.4%)	5 (15.2%)
VAS Pain Intensity (mm)		(n=31)
Mean (SD)	60.7 (12.20)	65.6 (18.88)
Median	61.0	66.0
Range	39 – 86	30 – 100
Symptom Severity, N (%)		
Mild	0	1 (3.0%)
Moderate	30 (85.7%)	22 (66.7%)
Severe	5 (14.3%)	10 (30.3%)

Data source: Section 14, Table 14.6 of the LEVP 2005-1/A CSR (see Module 5.3.5.1)
mm=millimeters (0-100)

Numbers analysed

Table 11. Datasets Analyzed for Efficacy (LEVP2005-1/Part A)

Datasets	Cinryze	Placebo	Total
All Randomized (ITT) Dataset	36	35	71
Efficacy Dataset	35	33	68

Outcomes and estimation

For the primary efficacy endpoint 'Time to start of unequivocal relief', in approximately 33% of subjects in the Cinryze treatment group relief started by 1 hour, and over 50% of the subjects had relief by 2 hours. Approximately 60% of subjects had relief as measured at 3 hours and 4 hours. In the placebo treatment group, the percentage of subjects with relief was lower at each time point (1 hour, 2 hour, 3 hour and 4 hour, approximately 15%, 33%, 37% and 44%, respectively).

The result is statistically borderline for the ITT dataset (p=0.048) while more pronounced for the Efficacy dataset (p=0.017).

Figure 4. Time to Start of Unequivocal Relief of Defining Symptom (ITT Dataset LEVP 2005-1/A)

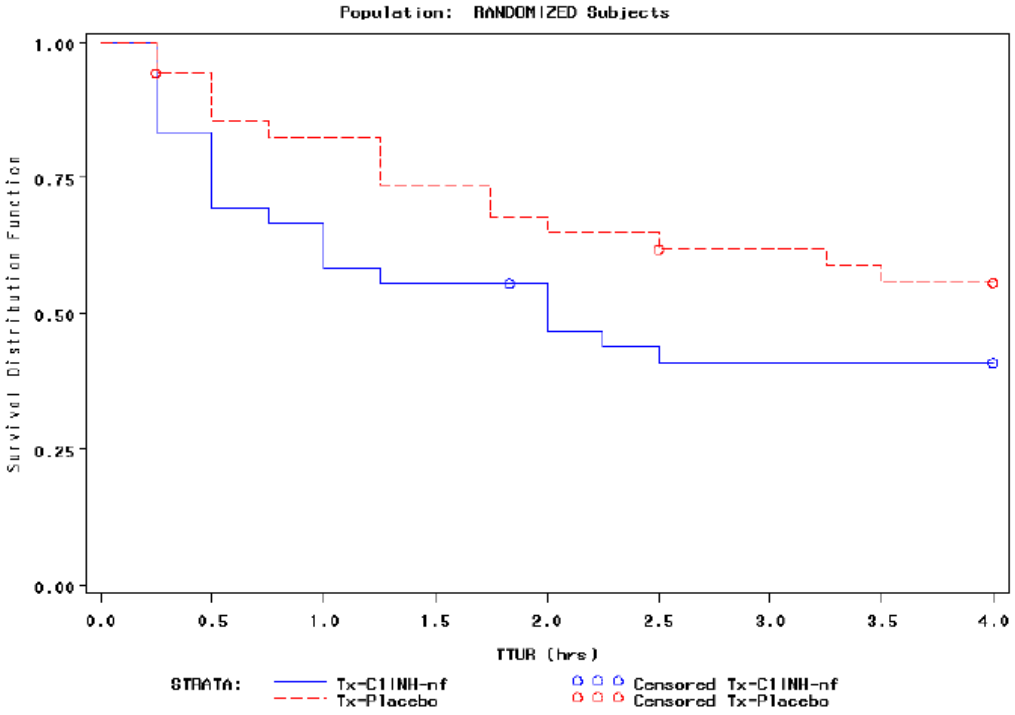
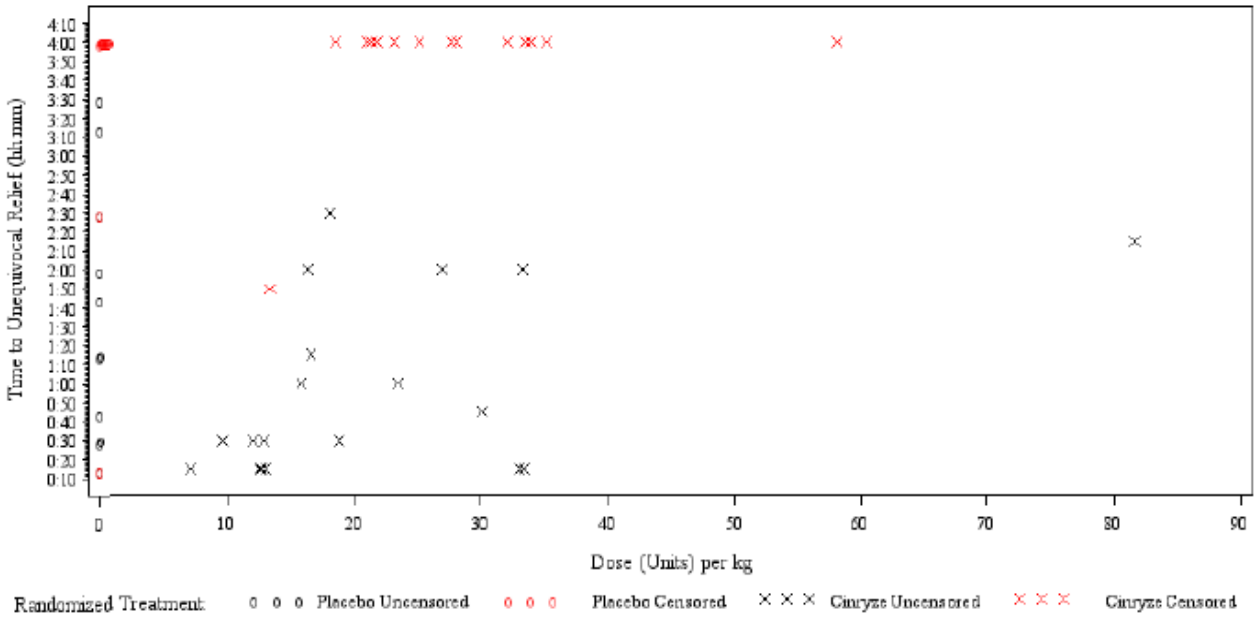


Table 12. Time to Beginning of Unequivocal Relief of the Defining Symptom (ITT and Efficacy Datasets LEVP 2005-1/A)

	Cinryze	Placebo
ITT dataset	36	35
N (%) of subjects with beginning of unequivocal relief of the defining symptom within 4h	21 (58.3%)	15 (42.9%)
Median time to beginning of relief (hrs) (95%-CI)	2.0 (1.0, NA)	NA (2.0, NA)
Hazard ratio (95%-CI)	2.048 (1.008, 4.164)	
p-value	0.048	
Efficacy dataset	35	33
N (%) of subjects with beginning of unequivocal relief of the defining symptom within 4h	21 (60.0%)	14 (42.4%)
Median time to beginning of relief (95%-CI)	2 (0.8, NA)	NA (2.0, NA)
Hazard ratio (95%-CI)	2.407 (1.171, 4.948)	
p-value	0.017	

Upon request from the CHMP, evaluation of the primary efficacy parameter in relation to dose per kg bodyweight was performed and revealed no correlation.

Figure 5. Study LEVP 2005-1/A: Time to Unequivocal Relief versus Dose (Units) per kg within 4 hours



Note that both first (initial) & second doses (if applicable) are used in calculating dose per kg, i.e., 'Units per kg'= sum of both dose amounts divided by the subject's body weight.
Only including subjects who received at least one dose of double-blind medication. Subjects who received open-label only are excluded.
Subject 14-002 is excluded from this plot because weight was not recorded for the subject.

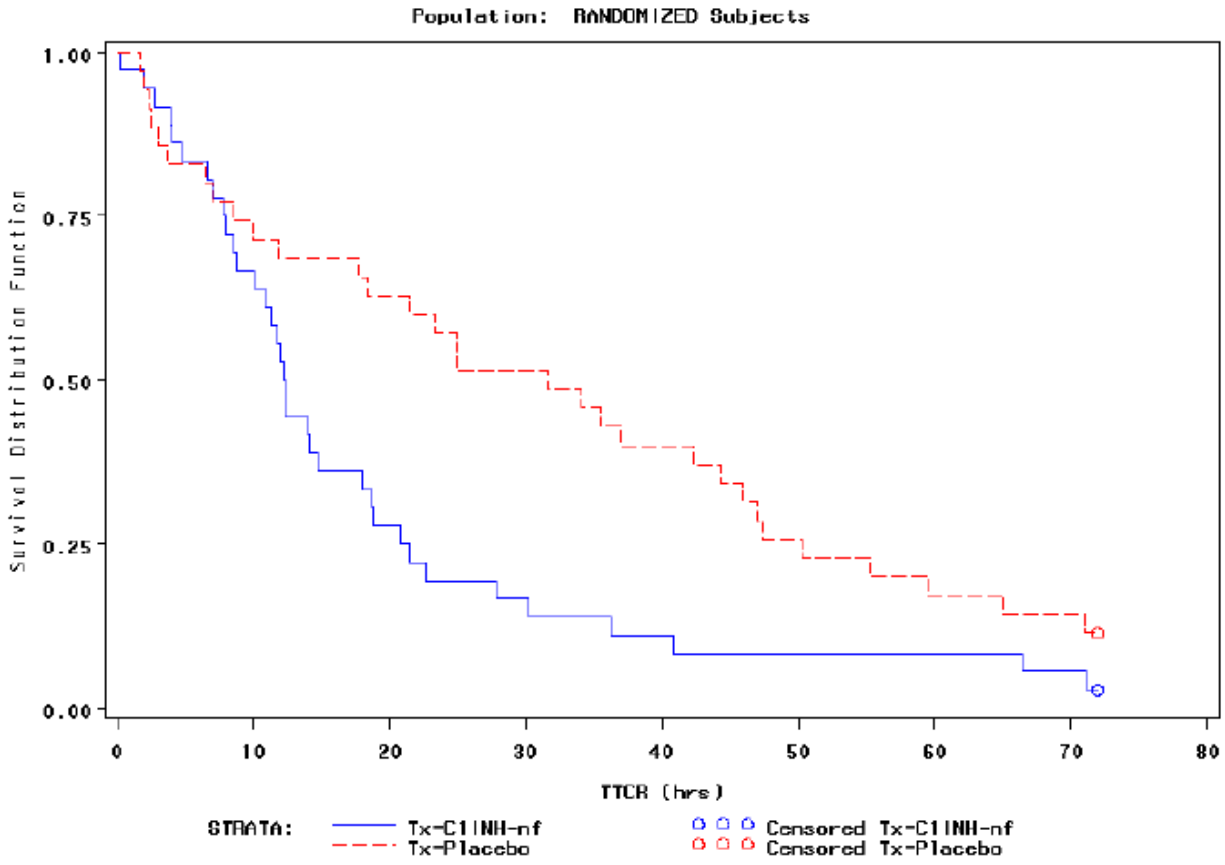
With regard to secondary efficacy endpoints, the percentage of subjects with beginning of relief within 4 hours was in favour of Cinryze with 60.0 % compared to 42.4 % with placebo, but this difference was not statistically significant.

Table 13. Number (%) of Subjects with Start of Unequivocal Relief of Defining Symptom within 4 hours Post-Infusion (Efficacy Dataset LEVP 2005-1/A)

	Cinryze n (%)	Placebo n (%)
Efficacy		
Yes	21 (60.0)	14 (42.4)
No	14 (40.0)	19 (57.6)
RR (95%-CI)	1.41 (0.87, 2.29)	
p-value	0.062	

A statistically significant difference was found for the time to complete resolution of the attack, which was in the median 12.3 hours after Cinryze therapy and 31.6 hours after placebo.

Figure 6. Time to complete resolution of the HAE attack (ITT dataset, Study LEVP 2005-1/A)



Ancillary analyses

While the difference in subject visual analogue scale (VAS) ratings was not statistically significant (p=0.085), the mean values showed improvement in the Cinryze treatment group and deterioration in the placebo treatment group, which suggests a possible pain improvement in the Cinryze treatment group as compared to placebo treatment group.

Table 14. VAS Sum of Pain Intensity Differences for 0-4h Post-Infusion: Efficacy Dataset LEVP 2005-1/A

Statistic	Cinryze N=35	Placebo N=33
n	35	31*
Mean[a]	54.9	-15.5
Difference in Means (95% CI)	70.5 (-10.0, 151.0)	
p-value	0.085	

[a]Adjusted for study center.
*2 placebo subjects pre-treatment VAS were not measured, which resulted in a missing SPID score.
Data Source: Section 14, Table 14.11

Fifteen subjects had a total of 18 laryngeal attacks and were treated with open-label Cinryze. Of these subjects, none required hospitalization or intubation.

About 40 % of subjects needed rescue treatment despite having received the full dose of 1000 U plus additional 1000 U of Cinryze.

Table 15. Cinryze infusions as study treatment and as rescue treatment (ITT Dataset LEVP 2005-1/A)

Category	Cinryze N (%)	Placebo N (%)
ITT Dataset, N	36	35
1 infusion of randomized study drug	12 (33.3%)	5 (14.3%)
2 infusions of randomized study drug	9 (25.0%) [a]	7 (20.0%)
2 infusions of randomized study drug followed by rescue with Cinryze	15 (41.7%)	20 (57.1%)
1 infusion of randomized study drug followed by rescue with Cinryze	0	1 (2.9%) [b]
2 infusions of randomized study drug followed by open-label Cinryze	0	1 (2.9%) [c]
1 infusion of randomized study drug followed by Cinryze administered in error	0	1 (2.9%) [d]

Study LEVP 2005-1/Part B

Methods

Study LEVP 2005-1/Part B was a Phase 3, randomized, double-blind, placebo-controlled, multicentre, crossover study to evaluate the safety and efficacy of Cinryze for the prevention of HAE attacks.

Study Participants

All subjects enrolled in Part B had been enrolled in Part A or met the inclusion criteria of Part A. The subjects selected for enrollment in Part B were those with relatively frequent angioedema attacks (at least 2/month on average), age ≥ 6 years, normal C1q level, documented HAE (low C4 level and one of the following criteria: low C1NH antigenic level or, normal C1 INH antigenic level and a low C1 INHC1 INH functional level or, a known HAE-causing C1 INHC1 INH mutation). Before inclusion in part B, the subjects were again assessed for the inclusion and exclusion criteria of Part A.

Treatments

Subjects could be randomized to a sequence Cinryze/Placebo (Cinryze 1000 U intravenously every 3 to 4 days for 12 weeks, followed by placebo intravenously every 3 to 4 days for 12 weeks) or Placebo/Cinryze (the opposite sequence). Prior to surgical interventions 1000 Units of Cinryze were administered. Acute laryngeal attacks were treated with open-label Cinryze (1000 Units initially and after 60 minutes, if necessary, another 1000 Units), which could be also administered in other attacks at Investigator's discretion.

Dose of 17-alpha-alkylated androgens or epsilon-aminocaproic acid had to be stable during Part B, but could be decreased before entry in Part B of the study, in which case the entry was postponed for a month.

Objectives

To evaluate safety and efficacy of Cinryze for the prevention of HAE attacks.

Outcomes/endpoints

Subjects were given diary cards and instructed to evaluate symptoms over the prior 24 hours.

Primary efficacy endpoint was number of HAE attacks during each therapy period (Cinryze vs. placebo) . Number of attacks was determined based on entries in diary cards by subjects and additionally by at least weakly evaluation by study personnel.

Secondary efficacy endpoints included:

- Average severity of attacks during each therapy period
- Average duration of attacks during each therapy period
- Number of open-label Cinryze infusions during each therapy period
- Number of days of swelling

Sample size

Based on the assumption of an angioedema attack rate of 1 every 2 weeks during placebo treatment vs 1 every 12 weeks in the prophylactic Cinryze phase, it was calculated that 10 subjects per sequence would provide more than 90% power to detect the treatment effect (Type I error: 0.05, 2-sided). Therefore, a total of 20 subjects was planned to be included.

Randomisation

Eligible subjects were randomized in a 1:1 allocation ratio to one of the two treatment sequences 'C1 INHC1 INH/placebo' and 'placebo/C1 INHC1 INH'.

Blinding (masking)

Study was double-blinded for the sequence of treatments.

Statistical methods

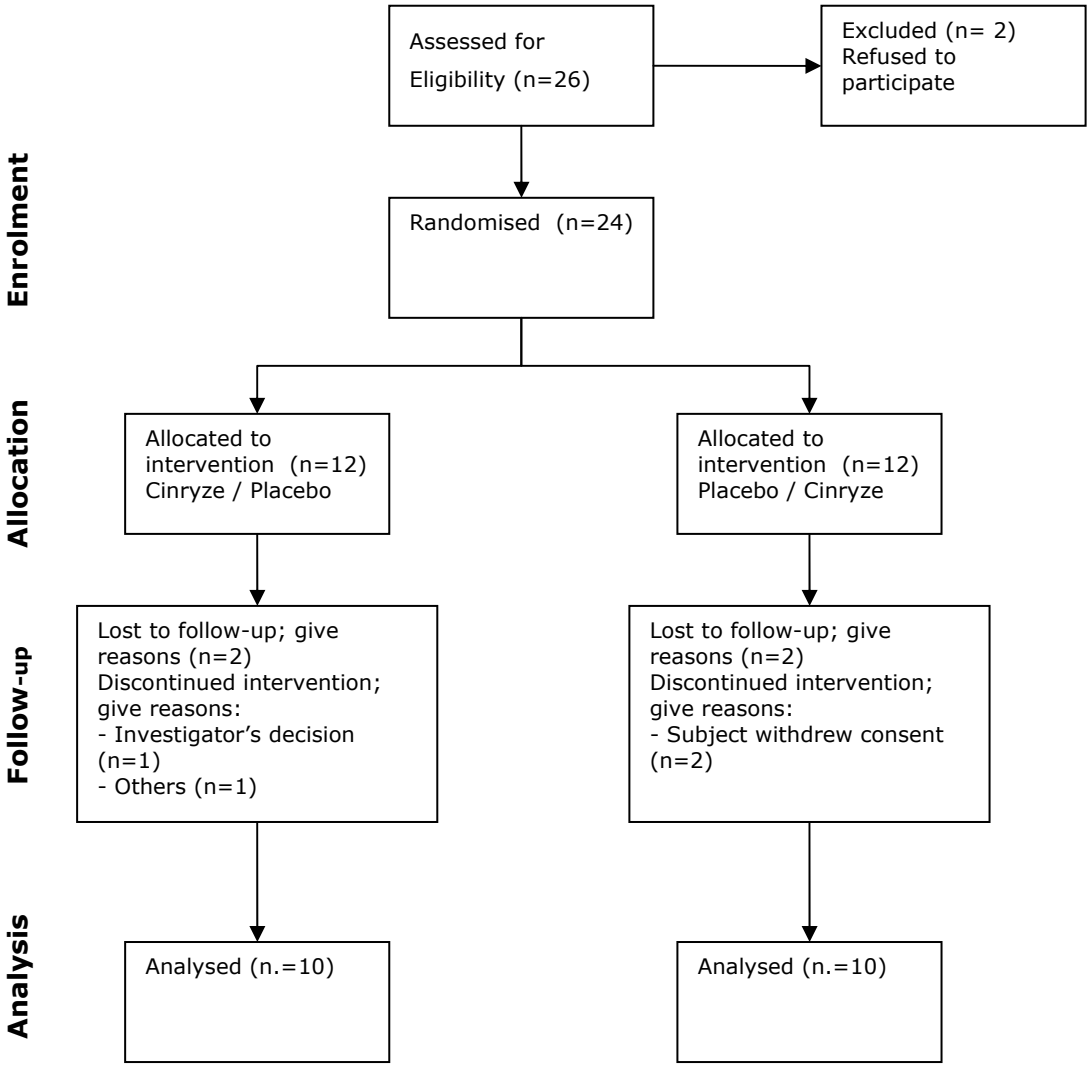
A generalized linear model was planned to compare the number of attacks of angioedema during each treatment period, normalized for the number of days the subject participated in that period. Anticipating Poisson distributed data the GEE method as implemented in the SAS statistical procedure PROC GENMOD was used.

Secondary parameters were compared by means of Fisher's exact test (number of subjects dropping out at each treatment period) or a Wilcoson Signed Rank test in case of continuous or ordinal variables (e.g. average severity of attacks, average duration of attacks).

The Efficacy Dataset consisted of all subjects randomized into one of two therapy sequences, who completed dosing in Period 1 and received at least one dose of study drug in the crossover phase, Period 2.

Results

Participant flow



Recruitment

Patients were recruited in 15 centres in the US. The first subject was enrolled into the study on 14 March 2005, the last patient completed the study on 22 August 2007.

Conduct of the study

There were 3 protocol amendments, but none of them concerned part B of the Protocol.

Baseline data

Table 16. Demographic characteristics (Efficacy Dataset Study LEVP 2005-1/B)

Variable	Statistic	Treatment Sequence		Total (N=22)
		Cinryze/Placebo (N=11)	Placebo/Cinryze (N=11)	
Age (years)	n	11	11	22
	Mean	41.7	34.5	38.1
	SD	19.27	14.76	17.16
	Median	40.0	35.0	38.5
	Range	14/73	9/64	9/73
Gender, n (%)	Male	2 (18.2)	0	2 (9.1)
	Female	9 (81.8)	11 (100.0)	20 (90.9)
Ethnic Origin n (%)	White/Caucasian	10 (90.9)	11 (100.0)	21 (95.5)
	Black/African American	1 (9.1)	0	1 (4.5)
	Hispanic/Latino	0	0	0
	Asian	0	0	0
	Native Hawaiian or Pacific Islander	0	0	0
	American Indian or Alaska Native	0	0	0
	Other	0	0	0
Weight (kg)	n	9	9	18
	Mean	70.48	76.34	73.41
	SD	9.246	25.647	18.944
	Median	70.50	64.30	69.25
	Range	58.1/87.1	37.6/113.9	37.6/113.9
Height (cm)	n	9	9	18
	Mean	166.17	163.17	164.67
	SD	6.892	8.722	7.780
	Median	165.10	160.00	165.10
	Range	152.4/177.8	149.0/175.3	149.0/177.8

Data Source: Section 14 Table 14.2.2 and Appendix 16.2 Listing 16.2.4

Table 17. Historical severity of symptoms: subjects with severe symptoms (Safety Dataset LEVP 2005-1/B)

Area of Swelling	Treatment Sequence		Total (N=24)
	Cinryze/Placebo (N=12)	Placebo/Cinryze (N=12)	
Extremities	4 (33.3)	6 (50.0)	10 (41.7)
Abdominal	9 (75.0)	10 (83.3)	19 (79.2)
Genitourinary	5 (41.7)	4 (33.3)	9 (37.5)
Facial	6 (50.0)	5 (41.7)	11 (45.8)
Laryngeal	8 (66.7)	6 (50.0)	14 (58.3)
Other	2 (16.7)	0	2 (8.3)

Data Source: Section 14 Table 14.5

Numbers analysed

24 subjects were randomised. Two subjects were excluded from the Efficacy Dataset (n=22) because they failed to complete the first arm of the study and did not cross over to receive at least one treatment in the second arm of the study.

Outcomes and estimation

Efficacy results in study LEVP2005-1/B are provided in the table below.

Table 18. Effect on HAE attacks (Efficacy dataset LEVP2005-1/B)

Parameter		Cinryze (n=22)	Placebo (n = 22)	p-value
Number of attacks	Mean (SD) Range	6.1 (5.43) 0 – 17	12.7 (4.80) 6 – 22	< 0.0001
Severity of attacks	Mean (SD) Range	1.3 (0.85) 0 – 3	1.9 (0.35) 1 – 3	0.0008
Duration of attacks (days)	Mean (SD) Range	2.1 (1.13) 0 – 4	3.4 (1.39) 2 – 8	0.0004
Number of open label infusions	Mean (SD) Range	4.7 (8.66) 0 – 36	15.4 (8.41) 2 – 34	< 0.0001
Days of swelling	Mean (SD) Range	10.1 (10.73) 0 – 38	29.6 (16.90) 8 – 67	< 0.0001

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial LEVP 2005-1/Part A

Title: LEVP 2005-1/Part A CHANGE Trial (C1-Inhibitor in Hereditary Angioedema Nanofiltration Generation evaluating Efficacy): A Double-blind, Placebo-controlled, Clinical Study to Investigate the Efficacy and Safety of C1 INH-nf (Cinryze), Purified C1 Esterase Inhibitor (Human) for the Treatment of Hereditary Angioedema (HAE) in Acute Attacks (Part A)			
Study identifier	Protocol: LEVP 2005-1 Study: LEVP 2005-1/Part A		
Design	Randomized, placebo-controlled, multi-center (USA), double-blind study designed to evaluate the efficacy and safety of Cinryze as a therapeutic agent for acute attacks of HAE.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		single-dose administration N/A N/A
Hypothesis	Superiority		
Treatments groups (1:1)	Cinryze		Treatment: Cinryze 1000U infusion Number randomized: 36
	Placebo		Treatment: Placebo Number randomized: 35
Endpoints and definitions	Primary endpoint	Time to relief	Time to the start of unequivocal relief of defining symptom (hours)
	Secondary endpoint	% relief 4h	Percentage of subjects with unequivocal relief beginning within 4 hours following treatment
	Secondary endpoint	Resolution HAE attack	Time to complete resolution of the HAE attack (hours)
	Secondary endpoint	Pain	Pain intensity (VAS)
Database lock	Date of last subject completed: 13/04/2007		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population	Intent to treat (ITT) – all randomized subjects (for primary endpoint) Efficacy Dataset – subjects who had true HAE attacks (for primary and secondary endpoints)		
Descriptive statistics and estimate variability	Treatment group	Cinryze	Placebo
	Number of subject All randomized(ITT)	36	35
	Time to relief	2	NA
	% relief 4h	21 (58.3)	15 (42.8)
	Number of subject Efficacy dataset	35	33
	Time to relief	2	NA
	% relief 4h	21 (60.0)	14 (42.4)
	Resolution HAE attack	12.3	≥ 25.0
	Pain	54.9	-15.5*

Effect estimate per comparison	Primary endpoint: Time to relief	Comparison groups	Cinryze vs Placebo (1)
		Success Ratio (95% CI)	2.048 (1.008, 4.164)
		P-value (Proportional Hazards Regression Model (PHR))	0.048
	Primary endpoint: Time to relief	Comparison groups	Cinryze vs Placebo (2)
		Success Ratio (95% CI)	2.407 (1.171, 4.948)
		P-value (PHR)	0.017
	Secondary endpoint: % relief 4h	Comparison groups	Cinryze vs Placebo (2)
		Proportion Ratio (95% CI)	1.41 (0.87, 2.29)
		P-value (Cochran-Mantel-Haenszel (CMH))	0.062
	Secondary endpoint: Resolution HAE attack	Comparison groups	Cinryze vs Placebo (2)
		Success Ratio (95% CI)	2.460 (1.331, 4.546)
		P-value (PHR)	0.004
	Secondary endpoint: Pain	Comparison groups	Cinryze vs Placebo (2)
		Difference in Means (95% CI)	70.5 (-10.0, 151.0)
		P-value (ANOVA)	0.085
Notes	* Based on 31 patients as the VAS in 2 placebo subjects pre-treatment was not measured, which resulted in missing SPID scores; (1) ITT population; (2) Efficacy dataset		

Summary of Efficacy for trial LEVP 2005-1/Part B

Title: LEVP 2005-1/Part B CHANGE Trial (C1-Inhibitor in Hereditary Angioedema Nanofiltration Generation evaluating Efficacy): A Double-blind, Placebo-controlled, Clinical Study to Investigate the Efficacy and Safety of C1 INH-nf (Cinryze), Purified C1 Esterase Inhibitor (Human) for the Prevention of Hereditary Angioedema (HAE) Attacks		
Study identifier	Protocol: LEVP 2005-1 Study: LEVP 2005-1/Part B	
Design	Phase 3, randomized, placebo-controlled, multi-centre (USA), double-blind crossover trial to confirm the efficacy of prophylactic Cinryze in preventing acute attacks of angioedema in subjects with HAE. (Open-label rescue option).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks not applicable not applicable
Hypothesis	Superiority	

Treatments groups	Cinryze		Treatment/Duration: Cinryze 1000 U 2x/week first 12 weeks in arm A and last 12 weeks in arm B. Number of subjects: 12
	Placebo		Treatment/Duration: Placebo 2x/week last 12 weeks in arm A and first 12 weeks in arm B. Number of subjects: 12
Endpoints and definitions	Primary endpoint	Number of attacks	Number of attacks of angioedema during each treatment phase.
	Secondary endpoint	Days of swelling	Number of days of swelling (days)
	Secondary endpoint	Severity of attacks	Average severity of attacks
	Secondary endpoint	Duration of attacks	Average duration of attacks (days)
	Secondary endpoint	Number of open-label infusions	Number of open-label Cinryze infusions
Database lock	Date of last subject completed: 22/08/2007		

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**		
Analysis population and time point description	The Efficacy dataset included all subjects who were randomized into 1 of 2 treatment sequences and who completed the entire initial treatment phase and received at least 1 treatment in the crossover phase. Week 24.		
Descriptive statistics and estimate variability	Treatment group	Cinryze	Placebo
	Number of subjects	22	22
	Mean Number of attacks	6.1	12.7
	SD	5.43	4.80
	Mean Severity of attacks	1.3	1.9
	SD	0.85	0.35
	Mean Duration of attacks	2.1	3.4
	SD	1.13	1.39
	Mean Number of open label infusions	4.7	15.4
	SD	8.66	8.41
	Mean Days of swelling	10.1	29.6

	SD	10.73	16.90
Effect estimate per comparison	Primary endpoint: Number of attacks	Comparison groups	Cinryze vs Placebo
		P-value (ANOVA)	< 0.0001
	Secondary endpoint: Severity of attacks	Comparison groups	Cinryze vs Placebo
		P-value (ANOVA)	0.0008
	Secondary endpoint: Duration of attacks	Comparison groups	Cinryze vs Placebo
		P-value (ANOVA)	0.0004
	Secondary endpoint: Number of open label infusions	Comparison groups	Cinryze vs Placebo
		P-value (ANOVA)	< 0.0001
	Secondary endpoint: Days of swelling	Comparison groups	Cinryze vs Placebo
		P-value (ANOVA)	< 0.0001

Analysis performed across trials (pooled analyses and meta-analysis)

Upon request from CHMP, the Applicant provided data on pre-procedure administration of open-label Cinryze from studies LEVP 2005-1/A and LEVP 2006-1. Cinryze was administered prior to a total of 91 procedures across the clinical program (40 procedures in children and 51 procedures in adults). The majority of procedures (~55%) were associated with dental work and ~37% were associated with a wide variety of surgeries or interventional diagnostic procedures. Pre-procedure administration of Cinryze led to 98% rate of no HAE attacks within 72 hours after the dose.

Clinical studies in special populations

No dedicated studies were performed in special populations.

A total of 46 unique subjects below the age of 18 years (2-5 years: n=3; 6-11 years: n=17; 12-17 years: n=26) were included in the clinical study program, mainly in the open-label studies. In Study LEVP2006-1 the proportion of HAE attacks achieving unequivocal relief of the defining symptom within 4 hours after Cinryze treatment was comparable between the 22 children in the ITT-E Dataset (age range 2-17 years) and adults, with 89% and 86% of attacks achieving relief, respectively. In Study LEVP2006-4, the 23 children in the ITT-E Dataset (age range 3-17 years) reported a median monthly HAE attack rate of 3.0 (range 0.5-28.0) prior to enrolment, which was reduced to <0.7 (range 0-3.4) while on Cinryze prophylaxis. 87% of children reported an average of ≤1 attack per month, comparable to the benefit observed in adults in this study.

Supportive studies

Study LEVP 2006-1

Study LEVP 2006-1 was an open-label, single-arm, multicentre study to evaluate the safety and efficacy of repeat use of Cinryze for the treatment of HAE attacks. Subjects were treated with open-label Cinryze for multiple HAE attacks (including all laryngeal attacks and gastrointestinal, facial, genitourinary, or extremity attacks) for the duration of the study. Dosing regimen was Cinryze 1000 U, which could be repeated after 60 minutes if there was no symptom relief. If a surgical or dental procedure was required short-term prophylaxis against HAE attacks could be performed at a dose of 1000 U within 24 hours of the surgical or dental procedure.

Of 609 attacks in 101 subjects, 68 % achieved unequivocal beginning of relief of the defining symptom (defined as 3 consecutive reports of improvement) within 1 hour after start of the first dose of Cinryze with a median time to beginning of relief of 0.75 hours. Within 4 hours, 87 % of patients achieved beginning of relief. Among 84 laryngeal attacks treated during this study, none required intubation following treatment with Cinryze.

Table 19. Proportion of attacks achieving unequivocal relief of the defining symptom within 1and 4 hours after start of the 1st dose of Cinryze (ITT dataset LEVP 2006-1)

ITT-E Dataset, N	Cinryze 101	
	Within 1 hour	Within 4 hours
Number of attacks with unequivocal relief	412/609 (67.7%)	529/609 (86.9%)
Proportion (%) of attacks with unequivocal relief by defining symptom		
Laryngeal	50/84 (59.5%)	65/84 (77.4%)
Gastrointestinal	245/353 (69.4%)	318/353 (90.1%)
Facial	35/72 (48.6%)	54/72 (75.0%)
Genitourinary	12/13 (92.3%)	13/13 (100%)
Extremity	70/86 (81.4%)	79/86 (91.9%)
Not specified	0/1	0/1

Data source: Section 2.7.3.3.2.2.1, Table 17 of Module 2.7.3 – "Treatment"

Using a less conservative definition of clinical relief of the defining symptom (*either* three consecutive assessments of improvement of the defining symptom *or* improvement of the defining symptom followed by cessation of symptom assessments), the proportion of HAE attacks with relief of the defining symptom within 4 hours was 95%.

Fifteen subjects were treated for at least 10 HAE attacks during the study with a maximum of 57 attacks. The median time to beginning of unequivocal relief was comparable among subjects who had up to 30 attacks during the study, ranging from 0.25 to 0.75 hours. Data demonstrate that the efficacy of Cinryze did not diminish with subsequent repeat administration.

A subgroup analysis of data from Study LEVP 2006-1 was performed upon request from the CHMP for subjects who received Cinryze treatment ≤4 hours (78 subjects with 366 attacks) or >4 hours (70 subjects with 237 attacks) after the onset of an attack.

- Subjects who received Cinryze treatment ≤4 hours after the onset of an HAE attack had a higher proportion of attacks achieving unequivocal relief of the defining symptom within 1 hour after start of the first dose of Cinryze compared to subjects who received treatment >4 hours after the onset of an attack (77% vs. 56%, respectively).

- The proportion of attacks achieving unequivocal relief within 4 hours was comparable regardless of the timing of treatment initiation (89% vs. 86%).

Study LEVP 2006-4

Study LEVP 2006-4 was an open-label, single-arm, multicentre study to evaluate safety and efficacy of repeat use of Cinryze for the prevention of HAE attacks. Subjects had to have a history of at least 1 HAE attack per month or a history of laryngeal oedema to be enrolled in the Study. Subjects could receive Cinryze in a dose of 1000 U every 3 to 7 days continuously for the entire duration of the study. Acute attacks could be treated with open-label Cinryze.

A median number of 3.0 attacks per month (range 0.08 – 28.0) was reported at screening. During prophylactic therapy with Cinryze, the median monthly attack rate per subject was reduced to 0.21 (range 0 – 4.56). Variability in the frequency of attacks over time is seen in HAE.

Overall, 12,019 Cinryze infusions were administered to a total of 146 study participants. In 46 subjects exposed to Cinryze for at least 1 year, the median monthly attack rate remained relatively constant.

Table 20. Frequency of HAE attacks per month (ITT-E dataset LEVP 2006-4)

	Cinryze
ITT-E Dataset, N	146
Monthly attack rate per subject [a]	
Mean (SD)	0.50 (0.754)
Median	0.21
Range	0-4.56
Distribution of monthly attack rate per subject, N (%) [a]	
0 attacks	51 (34.9%)
> 0 to ≤ 1 attack	75 (51.4%)
> 1 to ≤ 2 attacks	12 (8.2%)
> 2 to ≤ 3 attacks	5 (3.4%)
> 3 to ≤ 4 attacks	2 (1.4%)
> 4 attacks	1 (0.7%)

Data source: Section 2.7.3.3.2.2.1, Table 18 of Module 2.7.3 – "Prevention"

a: Monthly attack rate for each subject = 30.4 x (total # of attacks) / (last day of study drug – first day of study drug + 1)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In general design and conduct of main clinical studies fulfil the minimum requirements.

Existing potential comparator products either have well-established safety and tolerability issues, are unsuitable for significant proportions of the patient population (women and children), and/or are not approved widely across all EU member states at the time of conduct of pivotal trials. Therefore it is acceptable that in both pivotal trials placebo was used as a control.

The use of cross over design in the prophylaxis trial is deemed acceptable and the length of each treatment period suitable. Even though there is no wash-out period between the two therapies, this is not considered to be of major importance since subjects received open-label Cinryze for treatment of attacks and therefore potential bias is more likely to be in favour of placebo.

The use of open label Cinryze treatment and other rescue treatments in trials is acceptable for the concerned condition.

The endpoints chosen in both pivotal trials are considered satisfactory for HAE.

The decision to exclude from Efficacy dataset in study LEVP 2005-1/A patients based on whether they have low levels of C4 and is this not a 'true' episode is not supported, however, for the primary efficacy endpoint analysis the ITT dataset is provided.

Patients included in pivotal trials are deemed to in general represent the patients likely to receive the product within the agreed indication.

It was noted that the statistical model in study LEVP 2005-1/A for the submitted primary efficacy analysis deviated from the initial analysis model. While it is acknowledged that the recent analysis model is appropriate, it has to be kept in mind that this model was only used following unblinding of the data.

Overall, there are some limitations in the clinical study programme regarding representation of some age groups (particularly children) and the demonstration of the optimal doses, which will be addressed by the applicant in future studies. A PK/PD, safety and efficacy study in children less than 12 years of age is ongoing (Study No. 0624-203). Regarding optimal dosing in long-term prophylaxis further information is expected from an ongoing study with escalating doses in patients who are insufficiently protected by the currently recommended dosing (VP0624-400).

Efficacy data and additional analyses

The single pivotal study LEVP 2005-1/A supporting the indication for the treatment of acute HAE attacks showed result which are statistically borderline for the ITT dataset (p=0.048) while more pronounced for the Efficacy dataset (p=0.017). In this study a fixed dose regimen of 1000 U (irrespective of body weight) was applied. Based on these statistically weak results together with the need for a second dose at 60 minutes and for further rescue Cinryze treatment at 4 hours in 67% and 42% of subjects, respectively, the CHMP questioned the appropriateness of the proposed dosing regimen, particularly for patients with severe attacks.

Evaluation of additional PK data showed no correlation between PK parameters and applied dose normalized to body weight. No correlation between dose/kg and time to unequivocal relief of HAE attack was found in data from study LEVP 2005-1/Part A thus suggesting, that the amount of C1 INH administered does not directly influence the start of resolution from an attack. It has to be noted that for relief times more than one hour, the data represent mixed subjects having received a single or two separate doses and are therefore difficult to interpret. However, the lack of correlation supports the strategy of a simple, fixed dose regimen independent from body weight.

Therefore, taking into account also that clinical efficacy is shown for proposed dosage, a fixed dose regimen was considered acceptable by the CHMP. This is further substantiated by evidence that reaching certain concentration of C1 INH is not always necessary in order to prevent or treat HAE attacks.

In the open label study LEVP 2006-1 a higher efficacy was seen as compared to the pivotal study, however this can in part be explained by the inclusion of all kind of attacks of all locations and severities including milder attacks and the lack of censoring patients who received opiates. At the same time, this open label study results show that the proportion of attacks achieving unequivocal relief within 1 hour is lower for those with facial and laryngeal attacks, the latter being potentially life threatening. However, this effect had also been noted for other C1 INH products and may be caused by

the nature of the attack. Subgroup analysis of data from study LEVP 2006-1 also revealed that proportion of subjects who achieved unequivocal relief after 1 hour was lower, but after 4 hours similar in subjects who received Cinryze treatment > 4 hours after the onset of an HAE attack as compared to other subjects. This observation has been addressed in the SmPC with the recommendation to consider an earlier administration of a second 1000 U dose for patients experiencing severe attacks, particularly laryngeal attacks or if initiation of treatment is delayed. It is noted that recommending a higher single dose than 1000 U in such situations would not be substantiated by clinical efficacy data, but administering the second 1000 U dose earlier than 60 minutes apart from the first dose is reasonable, if required so by the clinical situation.

Regarding the prevention of HAE attacks, the results from the single pivotal study LEVP 2005-1/B supporting this claim demonstrated that during 12 weeks of prophylactic therapy with Cinryze the number, severity and duration of HAE attacks, the number of open label C1 INH infusions and the days of swelling were statistically significantly decreased in comparison to treatment with placebo.

The CHMP expressed its view that a more pronounced reduction of HAE attacks might have been achieved with a more optimized dosing regimen. In general, despite the results being statistically significant, from a clinical perspective the achieved halving of HAE attack frequency is not considered an optimal outcome. However, it should also be noted that this reduction of attack frequency was reached on top of the standard anti-angioedema therapy, which was continued concomitantly. Consequently, the CHMP requested the indication for long-term prophylaxis to be restricted to the most severely affected patients who have been unresponsive or intolerant to other prophylactic medication. Prophylaxis ideally should be of a limited duration with regular review by the prescribing doctor, therefore the proposed dose for routine prevention of 1000 Units of Cinryze every 3 or 4 days is approved as the recommended starting dose for routine prevention and the dosing interval may need to be adjusted according to individual response.

Short-term prophylaxis with C1 INH prior to a planned procedure is a more commonly used type of prophylaxis in HAE. Pre-procedural use of Cinryze has been applied in a total of 91 procedures across the clinical program. Cinryze was effective in preventing HAE attacks following 98% of medical, surgical, or dental procedures. Therefore the efficacy in short-term prophylaxis has been demonstrated.

Data from children below 12 years of age is scarce and is not sufficient to demonstrate appropriate efficacy. Therefore, the CHMP did not agree to the proposed use in the entire paediatric population. Considering that hormonal changes occurring during adolescence are triggers for HAE attacks and at this time patients can experience an increase in the intensity and severity of the disease, the CHMP agreed that a strict cut-off below the age of 12 years may not be appropriate when adolescence can start before 12 years of age hence accepting the use "in adults and adolescents".

2.5.4. Conclusions on the clinical efficacy

Available efficacy data for the indication of treatment of HAE attacks from the pivotal trial is of borderline significance. Taking into account also the additional support by further analyses there is however sufficient evidence of efficacy. It is noted that the overall dose finding is not optimal, however the CHMP considers based on the totality of the data that a fixed dose independent from body weight is acceptable, since efficacy is shown and there is no evidence that other dosing would be more efficient.

For long-term prophylaxis efficacy has been demonstrated to be statistically significant in all endpoints. In view of the limitation of the data, the indication was restricted to the most severely affected patients, who are intolerant to or insufficiently protected by other, less invasive prophylactic treatments, or patients who are unsuitable for on-demand therapy. Additional data from an ongoing

dose-escalating study in long-term prevention will become available and are requested to be provided post-licensure to further explore the optimal dose regimen.

Based on analysis of provided data, pre-procedure administration of Cinryze was effective in preventing HAE attacks.

Clinical data is currently only sufficient to support the use in adults and adolescents, but not a wider paediatric population.

2.6. Clinical safety

Patient exposure

Safety of Cinryze was monitored and assessed in all clinical trials of the development program. Open-label studies LEVP 2006-5 (PK), LEVP 2006-1 (treatment), and LEVP 2006-4 (prevention) were uncontrolled. Studies LEVP 2005-1/A (treatment) and LEVP 2005-1/B (prevention) were placebo-controlled. However, in Study LEVP 2005-1/B all subjects received open-label Cinryze at some point in time; therefore all AEs were attributed to Cinryze treatment.

Table 21. Patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled	109	96	96	0
Active -controlled	0	0	0	0
Open studies	286	286	140 (+ 146)**	46
Compassionate use	3	3		
Unique patients		262		

* At least 1 year on prophylactic therapy with Cinryze

** Dose range for 146 subjects in long-term prophylaxis was lower than proposed in SmPC

In total, approximately 14,500 doses of Cinryze have been administered to 262 unique subjects.

Adverse events

Most frequently reported AEs were infections/infestations, mostly considered to be unrelated to Cinryze.

Gastrointestinal disorders were the second most commonly reported types of TEAEs overall, in 90% of events considered to be unrelated to Cinryze. The only TEAEs in this SOC considered possibly, probably, or definitely related to Cinryze were uncommon events of nausea, vomiting, diarrhea, or abdominal pain.

Within skin and subcutaneous tissue disorders a total of 26 subjects reported rash at one or more times during the studies. However, determination of attribution to Cinryze is complicated since rash can be part of a prodrome or can occur during an HAE attack. In fact, 5 subjects had rash considered possibly, probably, or definitely related to Cinryze. None of these rashes were serious, and no rash led to discontinuation of study drug. Rash is the only Adverse Reaction occurring with common frequency; all other Adverse Reactions are uncommon. A review of all TEAEs describing pain, bruising, or rash at the injection/catheter site, or venous burning/phlebitis, etc., revealed an uncommon occurrence of

localized reactions to Cinryze infusions at the injection site with 24 such events in a total of over 14,500 infusions of Cinryze (0.2 % of infusions). Two of these events were considered severe.

Table 22. Commonly Reported TEAEs (LEVP 2006-5, LEVP 2005-1/A, LEVP 2006-1, LEVP 2005-1/B, and LEVP 2006-4)

	PK in HAE		HAE Treatment			HAE Prevention	
	2006-5 (OL)				2006-1 (OL)		2006-4 (OL)
	Cinryze		2005-1/A			2005-1/B	
SOC AE Preferred Term	Single Dose N=13	Double Dose N=14	Placebo N=12	Cinryze N=71	Cinryze N=113	Cinryze N=25	Cinryze N=146
Number (%) of subjects with ≥1 TEAE	**5 (38%)**	**1 (7%)**	**3 (25%)**	**10 (14%)**	**46 (41%)**	**20 (80%)**	**114 (78%)**
Infections and Infestations	**3 (23%)**	**1 (7%)**	**0**	**2 (3%)**	**17 (15%)**	**14 (56%)**	**89 (61%)**
Upper respiratory tract infection	1 (8%)	0	0	1 (1%)	2 (2%)	4 (16%)	33 (23%)
Nasopharyngitis	1 (8%)	1 (7%)	0	0	5 (4%)	2 (8%)	30 (21%)
Sinusitis	0	0	0	2 (3%)	6 (5%)	4 (16%)	20 (14%)
Bronchitis	0	0	0	0	3 (3%)	2 (8%)	16 (11%)
Urinary tract infection	0	0	0	0	2 (2%)	2 (8%)	17 (12%)
Pharyngitis streptococcal	1 (8%)	0	0	0	4 (4%)	0	8 (5%)
Gastroenteritis viral	0	0	0	0	0	2 (8%)	8 (5%)
Influenza	0	0	0	0	2 (2%)	1 (4%)	7 (5%)
Vulvovaginal mycotic infection #	0	0	0	1 (2%)	1 (1%)	1 (5%)	7 (6%)
Vaginal candidiasis #	0	0	0	0	0	1 (5%)	2 (2%)
Pharyngitis	0	0	0	0	1 (1%)	0	6 (4%)
Herpes simplex	0	0	0	0	1 (1%)	1 (4%)	5 (3%)
Viral upper respiratory tract infection	0	0	0	0	0	3 (12%)	2 (1%)

	PK in HAE		HAE Treatment			HAE Prevention	
	2006-5 (OL)				2006-1 (OL)		2006-4 (OL)
	Cinryze		2005-1/A			2005-1/B	
SOC AE Preferred Term	Single Dose N=13	Double Dose N=14	Placebo N=12	Cinryze N=71	Cinryze N=113	Cinryze N=25	Cinryze N=146
Gastrointestinal Disorders	**0**	**0**	**1 (8%)**	**2 (3%)**	**12 (11%)**	**8 (32%)**	**59 (40%)**
Nausea	0	0	1 (8%)	1 (1%)	2 (2%)	1 (4%)	29 (20%)
Vomiting	0	0	0	1 (1%)	0	2 (8%)	19 (13%)
Diarrhea	0	0	0	0	2 (2%)	1 (4%)	19 (13%)
Constipation	0	0	0	0	3 (3%)	1 (4%)	10 (7%)
Abdominal pain	0	0	0	0	0	1 (4%)	11 (8%)
Abdominal pain upper	0	0	0	0	1 (1%)	0	6 (4%)
Toothache	0	0	0	0	0	0	6 (4%)
Gastroesophageal reflux disease	0	0	0	0	2 (2%)	2 (8%)	2 (1%)
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**0**	**1 (1%)**	**6 (5%)**	**6 (24%)**	**41 (28%)**
Rash	0	0	0	0	3 (3%)	5 (20%)	18 (12%)
Contact dermatitis	0	0	0	1 (1%)	0	1 (4%)	5 (3%)
Urticaria	0	0	0	0	0	0	5 (3%)
Pruritus	0	0	0	0	0	2 (8%)	3 (2%)
General Disorders and Administration Site Conditions	**0**	**0**	**0**	**3 (4%)**	**1 (1%)**	**4 (16%)**	**32 (22%)**
Pyrexia	0	0	0	0	1 (1%)	1 (4%)	11 (8%)
Fatigue	0	0	0	1 (1%)	0	0	8 (5%)
Nervous System Disorders	**0**	**0**	**0**	**1 (1%)**	**3 (3%)**	**5 (20%)**	**42 (29%)**
Headache	0	0	0	0	1 (1%)	4 (16%)	28 (19%)
Respiratory, Thoracic, and Mediastinal Disorders	**0**	**0**	**0**	**0**	**6 (5%)**	**5 (20%)**	**37 (25%)**
Cough	0	0	0	0	3 (3%)	2 (8%)	13 (9%)
Pharyngolaryngeal pain	0	0	0	0	1 (1%)	1 (4%)	12 (8%)
Sinus congestion	0	0	0	0	2 (2%)	1 (4%)	6 (4%)
Postnasal drip	0	0	0	0	0	0	5 (3%)
Musculoskeletal and Connective Tissue Disorders	**1 (8%)**	**0**	**0**	**0**	**7 (6%)**	**5 (20%)**	**32 (22%)**
Back pain	1 (8%)	0	0	0	2 (2%)	2 (8%)	11 (8%)
Arthralgia	0	0	0	0	0	0	8 (5%)
Pain in extremity	0	0	0	0	0	2 (8%)	4 (3%)
Musculoskeletal chest pain	0	0	0	0	0	0	5 (3%)

	PK in HAE		HAE Treatment			HAE Prevention	
	2006-5 (OL)				2006-1 (OL)		2006-4 (OL)
	Cinryze		2005-1/A			2005-1/B	
SOC AE Preferred Term	Single Dose N=13	Double Dose N=14	Placebo N=12	Cinryze N=71	Cinryze N=113	Cinryze N=25	Cinryze N=146
Injury, Poisoning, and Procedural Complications	**0**	**0**	**0**	**0**	**5 (4%)**	**3 (12%)**	**29 (20%)**
Joint sprain	0	0	0	0	1 (1%)	0	6 (4%)
Muscle strain	0	0	0	0	0	0	6 (4%)
Limb injury	0	0	0	0	0	2 (8%)	1 (1%)
Congenital, Familial, and Genetic Disorders	**0**	**0**	**0**	**0**	**4 (4%)**	**2 (8%)**	**22 (15%)**
Hereditary angioedema	0	0	0	0	4 (4%)	2 (8%)	21 (14%)
Psychiatric Disorders	**0**	**0**	**0**	**1 (1%)**	**5 (4%)**	**1 (4%)**	**18 (12%)**
Anxiety	0	0	0	1 (1%)	2 (2%)	0	5 (3%)
Depression	0	0	0	0	1 (1%)	1 (4%)	5 (3%)
Vascular Disorders	**0**	**0**	**0**	**0**	**0**	**1 (4%)**	**13 (9%)**
Hypertension	0	0	0	0	0	0	5 (3%)
Reproductive System and Breast Disorders	**0**	**0**	**0**	**0**	**2 (2%)**	**1 (4%)**	**10 (7%)**
Dysmenorrhea #	0	0	0	0	0	0	6 (5%)
Vulvovaginal discomfort #	0	0	0	0	0	1 (5%)	0
Investigations	**0**	**0**	**0**	**2 (3%)**	**2 (2%)**	**1 (4%)**	**6 (4%)**
Blood pressure decreased	0	0	0	2 (3%)	0	0	0
Metabolism and Nutrition Disorders	**0**	**0**	**1 (8%)**	**1 (1%)**	**2 (2%)**	**1 (4%)**	**9 (6%)**
Blood and Lymphatic System Disorders	**1 (8%)**	**0**	**0**	**0**	**1 (1%)**	**2 (8%)**	**6 (4%)**
Pregnancy, Puerperium, and Perinatal Conditions #	**0**	**0**	**0**	**0**	**2 (3%)**	**0**	**6 (5%)**
Pregnancy #	0	0	0	0	2 (3%)	0	4 (4%)
Renal and Urinary Disorders	**0**	**0**	**0**	**0**	**1 (1%)**	**0**	**7 (5%)**
Eye Disorders	**0**	**0**	**0**	**0**	**0**	**2 (8%)**	**5 (3%)**
Immune System Disorders	**0**	**0**	**0**	**0**	**1 (1%)**	**0**	**5 (3%)**

Data Source: Module 5.3.5.3, Safety Data (Part 1), Tables 10.3.2.1.1.1 (LEVP 2006-1), 10.3.2.1.1.2 (LEVP 2006-4), 10.3.2.1.1.3 (LEVP 2005-1/A), and 10.3.2.1.1.4 (LEVP 2005-1/B); Section 2.7.4.2.1.3, Table 25 of Module 2.7.4 (LEVP 2006-5)

OL=open-label; # signifies a gender-specific SOC or term.

NOTE: A subject may have reported more than one TEAE or more than one TEAE per SOC.

Adverse events of special interest

Thrombosis

From clinical development five SAEs of thrombotic events have been reported, none of which was deemed causally related to study drug administration. Three further, non-serious, thromboembolic TEAEs occurred with one of them, a moderate thrombosis at port site, assessed as possibly related to the use of Cinryze. Further data on thromboembolic events derive from post-marketing exposure in the US. A total of 419 patients were treated for prevention of HAE attacks up to January 2010. During this reporting period, eight cases of thromboembolic events have been reported, thereof five as catheter-related venous thromboses. The Applicant assumes that approximately 25% of these patients had an

indwelling peripheral or central venous catheter. An estimated incidence for thrombotic events is 5/100 patients (5%).

Risk of transmission of infectious diseases

Data provide no evidence for viral transmission associated with Cinryze administration.

Potential risk of Adverse Events with self- or home-administration

The Applicant proposes that Cinryze could be used for self- or home-administration by selected patients. Appropriate selection and training of patients or caregivers by trained healthcare professionals should minimize the potential risk associated with this kind of use.

Serious adverse event/deaths/other significant events

Three deaths have been reported from open-labelled studies, none of which were considered by the investigator to be related to study drug. Further 40 subjects treated with Cinryze reported a SAE. Two of these SAEs (exacerbation of major chronic depression and musculoskeletal chest pain) were considered to have an unknown relationship to study drug. All other SAEs were considered unrelated to study drug.

Laboratory findings

There were no adverse trends in clinical laboratory results or vital signs following Cinryze infusions in the clinical studies.

Safety in special populations

Among the children adverse reactions with suspected relationship to treatment with Cinryze included headache, nausea, pyrexia, and infusion site erythema. None of these adverse reactions were severe, and none led to discontinuation of study drug. Overall, the safety and tolerability of Cinryze were similar in children and adults. However, the age group of 2-5 years old children represented by only 3 subjects is too small to establish safety in this paediatric subset.

Immunological events

Based on provided data from clinical studies, there is no evidence of clinically relevant anti-C1 INH antibody development. Nevertheless, Cinryze is a protein of human plasmatic origin and as such has an inherent immunogenic risk. Moreover, it is intended for repeated use or even a long-term prevention therapy. With increasing duration of the treatment the risk to develop neutralising anti-C1 INH antibodies may increase. Further data are expected from the ongoing Phase 4 study in the US.

Hypersensitivity reactions occurred in clinical studies with Cinryze: rash occurred commonly; contact dermatitis, erythema, and pruritus occurred uncommonly.

Safety related to drug-drug interactions and other interactions

Due to the human plasmatic origin, studies on metabolism or drug-drug interactions were not deemed necessary.

Discontinuation due to adverse events

No subjects were discontinued from study drug due to an AE in any of the clinical studies.

Post marketing experience

As of 27-Jan-2010, there were 300 post-marketing AE reports for Cinryze. The vast majority of reports (76%) described patients' underlying HAE (e.g., breakthrough HAE attacks with or without known trigger, or associated with non-labelled dosing regimens). Among the remaining reports not pertaining to HAE, the most common (>2 events) included headache, localized infusion site reaction (of any type), dizziness, fatigue, thrombotic events (of any type), nausea, peripheral oedema, abdominal pain, arthralgia, chest pain, vomiting, asthenia, back pain, blood glucose increased, liver function test abnormal, oropharyngeal pain, pain, pain in extremity, rash, and urticaria.

The updated post-marketing safety has provided reports which mainly relate to breakthrough attacks. The other main problems reported relate to thrombosis (DVT, catheter thrombosis, embolic stroke, jugular vein thrombosis and TIA). According to the Applicant the incidence of thrombotic events is 5 cases out of estimated 100 patients with indwelling cannulas in total. Additional reports such as central line infection highlight the problems associated with long-term intravenous catheters.

2.6.1. Discussion on clinical safety

Initially safety data was not presented as a function of length of time on treatment, which was corrected upon request from the CHMP. The main concern derives from post-marketing reports from the US, where thromboses and infection of intravenous catheters used in long-term prophylaxis have been reported.

A potential safety concern arises from the post-marketing data: risk of thrombosis within indwelling catheters *in situ* for long-term prophylaxis. It was observed at the incidence of 5 out of 100, which corresponds to the normal thrombotic risk of indwelling cannulae and therefore the risk is not likely to be increased by the administration of Cinryze.

Safety data about self-administration is scarce and only available from post-marketing reports in the US, where Cinryze is approved for long-term prevention therapy. However self-administration is likely to be used in actual clinical practice, therefore appropriate selection and training of patients or caregivers by trained healthcare professionals should be performed in order to minimize the potential risk associated with this kind of use. The most likely risks are related to the administration process itself (e.g. aseptic technique, venous access, needle disposal) as well as the handling of adverse drug reactions, particularly hypersensitivity.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

C1 INH when given as replacement therapy is not expected to have an adverse safety profile other than the known potential problems associated with any blood-derived product and possible AEs specific to any C1 INH, namely immunogenicity and thrombogenicity.

Off-label use of C1 INH at high doses had been associated with thrombosis, but this has not been observed in the presented clinical programme.

Risk of thrombosis within indwelling catheters *in situ* for long-term prophylaxis corresponds to the normal risk of indwelling cannulae. The Applicant will monitor thrombotic/thromboembolic events in clinical studies and post-marketing and report them regularly. In any case, the decision to start long-term prophylaxis has to be balanced very carefully in each individual case and should be restricted to severely affected patients who are intolerant to or insufficiently protected by oral prevention treatments or patients who are inadequately managed with repeated acute treatment.

An educational programme should be put in place for minimisation of risks associated with self-administration, which is likely to take place in actual clinical practice especially for long-term prophylaxis.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Important identified risks		
Thrombosis with high doses	Pharmacovigilance Reports of use in patients with these conditions will be closely monitored in any future clinical trials and in post-marketing surveillance and will be the subject of special review in PSURs and signal detection. A Phase 4 study evaluating doses of Cinryze higher than the currently approved dose also will monitor for thrombotic or thromboembolic events. A post-marketing registry to provide additional data on the safety and the use of Cinryze in the EU	The SPC contains the following warnings: 4.4 Special warnings and precautions for use "Thrombotic events have been reported in neonatal and infant subjects undergoing cardiac bypass procedures while receiving off-label high doses of another C1 INH product (up to 500 Units/kg) to prevent capillary leak syndrome. Based upon an animal study there is a potential thrombogenic threshold at doses greater than 200 Units/kg."
Transmission of infectious diseases	Pharmacovigilance	Nanofiltration and pasteurisation process during manufacturing. The SPC contains the following warnings: 4.4 Special warnings and precautions for use

		"Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens."
Important potential risks		
Thrombosis in patients with thrombogenic risk factors	Pharmacovigilance Reports of use in patients with these conditions will be closely monitored in any future clinical trials and in post-marketing surveillance and will be the subject of special review in PSURs and signal detection. A post-marketing registry to provide additional data on the safety and the use of Cinryze in the EU	The SPC contains the following warnings: 4.4 Special warnings and precautions for use "Patients with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely."
Development of C1 INH antibodies	Pharmacovigilance (reports of lack of efficacy or cases of known antibody development). The Phase 4 study includes assessments of C1 INH antibody at defined time points. Reports of use in patients with these conditions will be closely monitored in any future clinical trials and in post-marketing surveillance and will be the subject of special review in PSURs and signal detection. Antibody development will be	None applicable

	assessed during quarterly safety meeting data review. A post-marketing registry to provide additional data on the safety and the use of Cinryze in the EU	
Adverse events with self or home administration	Pharmacovigilance A post-marketing registry to provide additional data on the safety and the use of Cinryze in the EU	The SPC contains the following warnings: 4.4 Special warnings and precautions for use "There are limited data on the use of this medicinal product in home- or self administration. Potential risks associated with home-treatment are related to the administration itself as well as the handling of adverse drug reactions, particularly hypersensitivity. The decision on the use of home- treatment for an individual patient should be made by the treating physician, who should ensure that appropriate training is provided and the use reviewed at intervals." Development of a training programme for Health Care Professionals (HCP) to train patients on self administration of Cinryze. Educational materials for all patients/caregivers trained to self administer Cinryze.
Missing information		
Use in pre-adolescent children	Pharmacovigilance The Pediatric Committee has requested a clinical study in children (ages 2-12) and inclusion of children in the Phase 4 study. HAE is rarely diagnosed in children less than 2 years of age, there are no data in this age group. The Pediatric Committee has granted a waiver for conducting pediatric investigative studies in children less than 2 years of age.	Information in section 4.2 that the safety and efficacy of Cinryze in pre-adolescent children has not been established. Information in section 4.4 (see above) and in sections 4.8, 5.1, and 5.2 of the SPC on use in the paediatric population

	A post-marketing registry to provide additional data on the safety and the use of Cinryze in the EU	
Use in pregnancy	Pharmacovigilance Additional data collection for all patients reporting pregnancy to include AE reports during pregnancy and outcome of the foetus. A post-marketing registry to provide additional data on the safety and the use of Cinryze in the EU	The SPC contains the following information: Section 4.6 Fertility, pregnancy and lactation "Data on a limited number of exposed pregnancies indicate no adverse effects of C1 inhibitor on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. No maternal or embryofoetal effects of treatment were observed in reproductive studies in rats at dose levels up to 28-times the recommended human dose (1000 Units) based on an average adult body weight of 70 kg. The potential risk for humans is unknown. Therefore, Cinryze should be given to pregnant women only if clearly indicated".
Use in non-Caucasian patients	Pharmacovigilance A post-marketing registry to provide additional data on the safety and the use of Cinryze in the EU	None applicable

The CHMP, having considered the data submitted in the MA application is of the opinion that the risk minimisation activities listed in section 2.3 are necessary for the safe and effective use of the medicinal product.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

Treatment with Cinryze resulted in increases in antigenic and functional C1 INH levels. The elimination was slow with a half-life of 56 hours, but no accumulation was observed with repetitive dosing in intervals of 3 to 4 days. Reproducible increases in functional C1 INH activity indicated consistent

pharmacokinetics over repeated Cinryze administrations. Biological activity of Cinryze was demonstrated by an increase of C4 levels in 12 hours after infusion of Cinryze which was statistically significant compared to treatment with placebo. These PK and PD data show that Cinryze is a functional C1 INH product.

Indication: treatment of angioedema attacks

In the submitted double-blind study the median time to beginning of unequivocal relief of defining symptom was shorter for subjects treated with Cinryze as compared to placebo (2 vs. >4 hours, p=0.048 in ITT dataset, p=0.017 in Efficacy dataset). Cinryze group had higher percentage of subjects with beginning of relief within 4 hours (60% vs. 42.4 % for placebo, difference not statistically significant) and shorter time to complete resolution of the attack (12 hours vs. ≥ 25 hours for placebo, difference statistically significant). These results are weaker than expected for a C1 INH product (e.g. expected median time to start of unequivocal relief of defining symptoms 0.83 hours), which may have been influenced by selection of study participants, characteristics of attacks included in the study, definition of primary endpoint and the use of a fixed dose without relation to body weight although an effect of body-weight adjusted dose on time to relief was not detected.

In the submitted open-label study a greater variety of subjects was enrolled presenting with HAE attacks of all locations and severities including laryngeal and extremities attacks, which had been excluded from the preceding double-blind trial. Of 609 attacks in 101 subjects, 68 % achieved unequivocal beginning of relief of the defining symptom within 1 hour and 87 % within 4 hours. The observed median time to beginning of relief of 0.75 hours is in line with the time to relief expected from literature data. Following treatment with Cinryze none of the 84 laryngeal attacks required intubation. Data in subjects with repeated attacks (up to 57 attacks) demonstrate that the efficacy of Cinryze does not diminish with repeated administration.

Indication: routine prevention of angioedema attacks

The results of a placebo-controlled cross-over study showed statistically significant reduction by 50% in the number of HAE attacks and reduced severity and duration of attacks as effects of a prophylactic therapy with Cinryze. Another, open-label study had a larger database (12,019 Cinryze infusions, 146 subjects in total, 46 subjects exposed to Cinryze for more than a year) and showed reduction of median monthly HAE attack rate from 3.0 to 0.21 attacks per month, which led to 86% of subjects on long-term prevention experiencing ≤1 HAE attack per month on average. The protective effect did not diminish over time.

Indication: pre-procedure prevention of angioedema attacks

Data from a total of 91 procedures show that pre-procedure administration of Cinryze was effective in preventing HAE attacks for 72 hours following 98% of medical, surgical, or dental procedures.

- Uncertainty in the knowledge about the beneficial effects.

Based on the available data it is not known, whether a higher initial dose would have improved the efficacy in treating HAE attacks. In the pivotal trial in acute treatment 66% of patients received a second 1000 U dose due to insufficient response. The administration of a sufficient initial dose is essential for the treatment of attacks, especially when the attack is severe. The subjects who required a second 1000 U dose more often had a severe, especially a laryngeal attack or had a lag time of more than 4 hours between onset of attack and Cinryze administration. It was therefore agreed to amend the dose recommendation for patients experiencing severe attacks, particularly laryngeal attacks, or if initiation of treatment is delayed, that consideration should be given to an earlier administration of a second 1000 U dose for these cases. A post-marketing registry will specifically monitor cases of laryngeal attacks and initiation of treatment more than 4 hours after the onset of the attack.

It is also unknown, whether a permanently higher C1 INH levels resulting from an intensified replacement therapy with exogenous C1 INH could outweigh the influence of the attack triggering factors in HAE patients. The impact of such higher doses of exogenous C1 INH on the complement and contact activation system cannot be anticipated. Breakthrough attacks occurred despite routine prevention therapy, making on-demand treatment necessary, which indicated a risk of insufficient efficacy of long-term prophylaxis. The dose regimen for the long-term prophylaxis was discussed. While the SmPC proposes 1000 U every 3 to 4 days, a schedule of 1000 U every 3 to 7 days was in general used in the long-term study. It was agreed that the dosing interval may need to be adjusted according to the individual response. The Applicant will report results from Study VP 0624-400, a dose escalating study in the prophylactic therapy with Cinryze, as soon as available.

There is insufficient data on pharmacokinetics, safety and efficacy in children below the age of 12 years hence the CHMP did restrict the indication to the use in adults and adolescents.

Risks

- Unfavourable effects

Adverse events reported from clinical studies were mostly considered to be unrelated to treatment with Cinryze. A commonly reported adverse reaction was rash. All other adverse reactions were reported with uncommon frequency: hyperglycemia, dizziness, headache, venous thrombosis, phlebitis, venous burning, hot flush, cough, nausea, vomiting, diarrhoea, abdominal pain, contact dermatitis, erythema, pruritus, joint swelling, arthralgia, myalgia, injection site rash/erythema, infusion site pain, chest discomfort, and pyrexia.

Localized reactions to Cinryze occurred uncommonly with a frequency of 0.2 % of administrations. Based on provided data from clinical studies, there is no evidence of clinically relevant anti-C1 INH antibody development.

For the long-term prophylaxis indication, additional risks relate to frequent venous access and the use of intravenous catheters with the risks of thrombosis and infection. A venous thrombosis of the port was reported and assessed as possibly related to administration of Cinryze. Post-marketing data from prophylactic therapy in 419 patients have eight cases of thromboembolic events reported, thereof five as catheter-related venous thromboses. This corresponds to the normal thrombotic risk of indwelling cannulas and is not increased by the administration of Cinryze. The potential risk of thrombosis in patients with thrombogenic risk factors has been addressed in the Risk Management Plan. The Applicant is currently performing a Phase 4 study, where thrombogenic and immunogenic risk are further investigated.

- Uncertainty in the knowledge about the unfavourable effects.

In clinical studies with other C1 INH products time to relief had to be awaited without the option of an additional dose after one hour. Due to the double-blind design with the comparator treatment placebo and possibility to administer second dose, there is a risk that investigators may have tended not to await the relief of the attack but rather administer a second dose. It is uncertain whether the patients who received a second 1000 U dose in the treatment of acute attacks really needed this dose, or whether the attack would have resolved without this additional dosing.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

Hereditary angioedema is a serious, debilitating, and potentially fatal disease caused by a rare autosomal dominant mutation on chromosome 11 that leads to a decrease in C1 INH activity. Attacks range in severity from mild to severe, with GI involvement causing nausea, vomiting, and diarrhoea, or may even mimic an acute surgical emergency. Laryngeal swelling can be life threatening and these attacks account for the mortality risk described for HAE. Hence, HAE attacks require prompt treatment, often in an emergency room. Optimal management of C1 INH deficiency should include treatment of acute attacks, short-term prophylaxis and long-term prophylaxis in order to minimise the frequency and severity of recurrent attacks.

The benefits from the therapy with Cinryze have been demonstrated in treatment and prevention of HAE attacks and assure that Cinryze in general is effective in the agreed indications.

The identified unfavourable effects and risks are in general in line with those of other C1 INH products and therefore do not raise any major concerns in the agreed indications.

The lack of data in paediatric population below 12 years of age remains an important source of concern for safe and efficient use of Cinryze in this patient population, therefore it has to be addressed before extending the indication to children below 12 years of age.

From the available data it is not known, whether a higher initial dose would have improved the efficacy in treating HAE attacks and whether a permanently higher C1 INH levels resulting from an intensified replacement therapy could prevent more HAE attacks. Further research for determination of the optimal dose is recommended, but it has to be noted that the efficacy is shown also at the proposed doses.

- Benefit-risk balance

The overall benefit risk balance of Cinryze is considered positive in the agreed indications in adults and adolescents.

2.8.1. Discussion on the benefit-risk balance

Initially, the applicant proposed the therapeutic indication "Treatment and prevention of angioedema attacks in adults, adolescents and children with C1 inhibitor deficiency" for Cinryze. The proposed dose regimen was a fixed dose of 1000 U.

The overall quality of the drug product has been demonstrated. Although the product is controlled by adequate test methods and specifications, the applicant should tighten some finished products specifications and should include additional specifications for purity and for the recently identified impurities and should calibrate in-house reference material against the WHO international standard in order to ensure the continuous consistency of the potency and purity of the product.

Available efficacy data for the indication of treatment of HAE attacks from the pivotal trial is of borderline statistical significance. Taking into ac count also the additional support by further statistical analyses there is however sufficient evidence of efficacy in this study. The efficacy was better in the open-label trial, where milder cases were also included and subjects who received opiates for pain were not censored. The discussion whether a faster onset of relief could be attained with an adjusted dose regimen together with a review of all available data with Cinryze and other plasma derived C1 INH products led to the view that mainly subjects who presented with severe, especially with laryngeal attacks, and those who started Cinryze treatment after a more than 4 hours delay after attack onset,

were more likely to be in need of a second 1000 U dose one hour after the first dose. It is therefore suggested to consider an earlier administration of the second 1000 U dose (not having to wait for 60 minutes between both doses) in this subgroup of attacks. This approach of a situation-adapted administration of the second 1000 U dose is considered appropriate to ensure adequate and rapid treatment for those with severe attacks or those who have a delayed presentation and is justified on the basis of the available data. Further experience will be generated through a post-marketing registry, which will monitor available information on severe and laryngeal attacks as well as cases where treatment started later than 4 hours after onset of attack. Supportive of a beneficial effect in the treatment of acute attacks are the consistency of the favourable effects in all, the primary and secondary endpoints together with the absence of relevant safety concerns in the pivotal and open-label studies with Cinryze and the longstanding experience with the use of a preceding C1 INH preparation.

When used as pre-procedural prevention, the available data from a dedicated analysis confirms the efficacy and safety of Cinryze.

For the use of Cinryze in long-term prophylaxis, a clear evidence of efficacy was found in terms of the frequency, severity and duration of attacks and the number of days of swelling, all of which were significantly reduced. However, during evaluation it has been questioned, whether a higher than ~50% reduction of the number of attacks, as shown in the presented pivotal trial, could be reached with an intensified dose regimen. Based on available data the potential effects of higher doses cannot be fully assessed. The problems of frequent IV access, the treatment burden of twice weekly infusions and the need for additional on demand therapy need to be weighed individually against the efficacy as demonstrated. This lies within the responsibility of the treating physician, who has to carefully balance the individual patient's quality of life, taking into consideration both the benefits and the burden of long-term therapy. The SmPC states that for routine prevention of attacks the dosing of 1000 Units every 3 to 4 days may need to be adjusted according to the individual response. Results from the ongoing dose escalation study in long-term prevention therapy in insufficiently controlled HAE patients are to be reported as soon as available. The risk of thrombosis at the injection site, especially when administered via an indwelling catheter, has to be further monitored. The indication for a long-term prophylactic therapy should, in the light of currently available data on efficacy and safety, will be restricted to the patients that are most likely to benefit from such prophylactic therapy – severely affected patients, who are intolerant to or insufficiently protected by oral prevention treatments or patients who are inadequately managed with repeated acute treatment. Regular review of the individual patients' benefit:risk balance will be performed by the prescribing physician, thereby ensuring that only those who have a positive B/R for long-term prophylaxis are maintained on therapy. Available data are insufficient to recommend a safe and effective dose for the treatment of children aged below 12 years, therefore the use of Cinryze is restricted to adults and adolescents.

At present no C1 INH product is approved in Europe for long-term prevention of HAE attacks. In addition, no C1 INH product is approved for pre-procedure prophylaxis throughout the EU. A marketing authorisation for Cinryze in the agreed indication would therefore add treatment options for HAE patients.

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concern as reflected in section 3.7.

Additional risk minimisation activities were also required and are reflected in section 2.3.

2.8.3. Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Cinryze is not similar to Icatibant (Firazyr) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit-risk balance of Cinryze in:

-treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with hereditary angioedema (HAE), and

-routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.

was favourable.

However, the CHMP notes that pursuant to the Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03), ViroPharma is to be considered as the same applicant/marketing authorisation holder as Sanquin, which holds marketing authorisations in a number of Member States for a medicinal product containing the same qualitative and quantitative composition in active substance(s), having the same pharmaceutical form and overlapping indication(s) as the above mentioned medicinal product. These particulars may preclude the granting of a marketing authorisation for the above mentioned medicinal product.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Cinryze not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Firazyr for the same therapeutic indication.