

CLINICAL PHARMACOLOGY REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125287/0/1

Sponsor: CSL Behring

Product: C1 Esterase Inhibitor (Human)

Indication: Hereditary Angioedema

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INTRODUCTION

C1 esterase inhibitor (C1INH) is a naturally occurring single chain glycoprotein in human blood. C1INH is a serine protease inhibitor and a member of the serine family. In its mature state, C1INH consists of 478 amino acids. The molecular weight of the heavily glycosylated molecule is 105 kDa, of which the carbohydrate chains comprise 26 -35%. It is mainly synthesized in the liver. Its main function is to regulate the activity of serine proteinases.

C1INH is indicated for the treatment of hereditary angioedema (HAE). HAE is a syndrome resulting from the heterozygous deficiency of endogenous C1INH, and this deficiency results in attacks of non-itching swellings of the skin or mucosa. In general, these swellings do not hurt, but acute attacks of angioedema may be life threatening if sites such as the larynx are affected, and angioedema is often associated with significant morbidity if it occurs in the gastrointestinal system. Hence, HAE attacks require prompt treatment, often in an emergency room.

Administration of an exogenously C1INH increases plasma levels of C1INH activity and temporarily restores the natural regulation of the contact, complement, and fibrolytic systems.

Beriner P is a highly purified, pasteurized, and lyophilized, C1-INH concentrate. After reconstitution with 10 mL physiological saline, the solution contains 50 Units per mL. Beriner P is supplied in vials containing approximately 500 Units. Beriner P seems to be effective and well tolerable in subjects with HAE both in acute attacks and prophylactically.

The sponsor, CSL Behring, has provided a pharmacokinetic study in their Biologics License Application (BLA). The data for the doctorate thesis were prospectively collected, in an open, uncontrolled, one center design. The project was prospectively designed for the analysis of C1-INH half-lives; additional pharmacokinetic analysis was performed retrospectively. Subjects underwent a 72 hours observation time with blood sampling for pharmacokinetics. Data on 40 subjects were provided to ----b(4)-----.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.3 Pharmacokinetics

The pharmacokinetics (PK) of [Trade Name] were evaluated in an open-label, uncontrolled, single-center study in 40 subjects (34 adults and 6 children under 18 years of age) with either mild or severe hereditary angioedema (HAE). The 25 subjects with mild HAE were treated on demand for an acute attack; the 15 subjects with severe HAE were treated on a prophylactic basis. All subjects received a single intravenous injection of [Trade Name] ranging from 500 U to 1,500 U. ~~The median dose was 1,058 U (range: 526-1,010 U), the median dose per kg body weight was 14.5 U/kg (range: 9.9-22.1 U/kg).~~ For pharmacokinetic study, blood ~~was sampled~~ samples were taken ~~to determine C1-INH activity~~ at baseline and for up to 72 hours after ~~the infusion~~ drug administration. ~~In addition, the *in vivo* recovery (IVR) was calculated for the first 4 hours after the infusion.~~ The median volume of distribution at steady state of [Trade Name] in all subjects was ~~45.4 mL/kg body weight, which corresponds to 3.2 L for a person weighing 70 kg.~~ The median systemic clearance was ~~1.0 mL/(kg per hour) (70 mL/h for a person weighing 70 kg),~~ resulting in an overall median elimination half life of 36.1 hours.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of Berinert were evaluated in an open-label, uncontrolled, single-center study in 40 subjects (35 adults and 5 children under 16 years of age) with either mild or severe HAE. The 25 subjects with mild HAE were treated on demand for an acute attack; the 15 subjects with severe HAE were treated on a prophylactic basis. All subjects received a single intravenous injection of Berinert ranging from 500 U to 1,500 U. For pharmacokinetic study, blood samples were taken at baseline and for up to 72 hours after drug administration. Pharmacokinetic parameters were estimated using non-compartmental analysis (with or without baseline adjusted). The following Table summarizes the pharmacokinetic parameters of Berinert in 35 adult patients with HAE.

**Pharmacokinetic parameters of Berinert in subjects with HAE
by non-compartmental analysis (n=35)**

Parameters	Unadjusted for baseline	Adjusted for baseline
AUC _(0-t) (hr x IU/mL)*	27.5 ± 8.5 (15.7-44.7)	12.8 ± 6.7 (3.9-34.7)
CL (mL/hr/kg)	0.60 ± 0.17 (0.34-0.96)	1.44 ± 0.67 (0.43-3.85)
V _{ss} (mL/kg)	18.6 ± 4.9 (11.1-27.6)	35.4 ± 10.5 (14.1-56.1)
Half-life (hrs)	21.9 ± 1.7 (16.5-24.4)	18.4 ± 3.5 (7.4-22.8)
MRT (hrs)	31.5 ± 2.4 (23.7-35.2)	26.4 ± 5.0 (10.7-33.0)

*based on 15 U/kg dose

Numbers in parenthesis are range

The following Table summarizes the pharmacokinetic parameters of Berinert in 5 children (6-13 years) with HAE. Based on adjusted baseline, compared to adults, the half-life of Berinert was shorter and clearance was faster in children. However, the clinical implication of this difference is not known.

**Pharmacokinetic parameters of Berinert in children with HAE
by non-compartmental analysis (n=5)**

Parameters	Unadjusted for baseline	Adjusted for baseline
AUC _(0-t) (hr x IU/mL)*	25.45 ± 5.8 (16.8-31.7)	9.78 ± 4.37 (4.1-15.2)
CL (mL/hr/kg)	0.62 ± 0.17 (0.47-0.89)	1.9 ± 1.1 (0.98-3.69)
V _{ss} (mL/kg)	19.8 ± 4.0 (16.7-26.1)	38.8 ± 8.9 (31.9-54.0)
Half-life (hrs)	22.4 ± 1.6 (20.3-24.4)	16.7 ± 5.8 (7.4-22.5)
MRT (hrs)	32.3 ± 2.3 (29.3-35.2)	24.0 ± 8.3 (10.7-32.4)

*based on 15 U/kg dose

Numbers in parenthesis are range

In-vivo recovery (IVR) was defined as the difference between the maximum concentration of C1INH during 4 hours after start of drug administration and the baseline C1INH level before drug administration. The mean incremental IVR of Berinert P in all subjects, children, adults, patients on prophylactic therapy, and patients on demand therapy was 2.6 ± 1.1, 2.2 ± 0.3, 2.7 ± 1.1, 3.2 ± 1.3, and 2.3 ± 0.7 %/U per kg body weight, respectively. Mean IVR was higher for subjects on prophylactic treatment compared to subjects with on-demand treatment.

Studies have not been conducted to evaluate the PK of Berinert in special patient populations identified by gender, race, geriatric age, or the presence of renal or hepatic impairment.

In their submission of July 23, 2009, the sponsor has accepted the FDA proposed clinical pharmacology labeling.

RECOMMENDATION

The pharmacokinetic study of C1 esterase inhibitor is acceptable and the sponsor should incorporate the clinical pharmacology labeling as suggested by the FDA.

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PHARMACOKINETIC STUDY

Study Title: Pharmacokinetics of C1 Esterase Inhibitor, human (pasteurized) in subjects with hereditary angioedema (HAE).

The data collected and analyzed in this report and submitted by the sponsor (CSL Behring) were derived from a doctorate thesis generated at the Children's Hospital of the Johann Wolfgang von Goethe University in Frankfurt, Germany.

There were 40 subjects with HAE. Thirty-one subjects were female and 9 were males. The age of the subjects ranged from 6 to 68 years (6 subjects were less than 18 years of age). Subjects with HAE either in an on demand treatment (mild HAE) or on a prophylactic treatment (receiving Berinert 2 to 3 times weekly, severe HAE) were included in the study. Subjects received doses of 500-1500 U of Berinert P. Six subjects (5 children and 1 adult) received 500 U of Berinert P, whereas one subject received 1500 U of Berinert P intravenously. Remaining subjects received 1000 U of Berinert P. The actual doses were determined by the potency of the respective batch of the dose and the nominal dose. Blood samples were collected just before drug administration and at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 16, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours after drug administration. C1-INH activity was analyzed by a $\beta(4)$ assay and C1-INH antigen was analyzed by $\beta(4)$. Plasma concentration vs time data were fitted to one compartment model. The model dependent pharmacokinetic parameters are summarized in Table 1. The half-life of Berinert p was shorter and clearance was almost twice in children than adults (Table 1). Although the half-life of Berinert p was 10 hours shorter in patients on prophylactic than on demand therapy but the clearance was comparable between the two groups (Table 2).

TABLE 1
Pharmacokinetic parameters of Berinert P in 40 subjects with HAE
following intravenous administration

Parameters	All (n =40)	Children (n = 6)*	Adults (n = 34)
AUC (U*h/mL)**	20.2 ± 16.2 (2.9-86.1)	13.4 ± 9.6 (2.9-29.4)	21.4 ± 16.9 (6.3-86.1)
Clearance (mL/h/kg)	1.1 ± 0.9 (0.2-5.2)	2.0 ± 1.8 (0.5-5.2)	1.0 ± 0.5 (0.2-2.4)
V _{ss} (mL/kg)	47.0± 11.9 (23.3-69.2)	50.5 ± 7.4 (41.6-62.3)	46.3 ±12.5 (23.3-69.2)
Half-life (hrs)	39.9 ± 21.8 (7.3-96.0)	31.5 ± 23.2 (7.3-70.5)	41.4 ± 21.6 (10.3-96)
MRT (hrs)	57.6 ±31.5 (10.5-138)	45.5± 33.5 (10.5-101)	59.7 ± 31.1 (14.9-138)

*under 18 years of age

** based on 15 U/kg dose

Mean ± SD, numbers in parenthesis are range

TABLE 2
Pharmacokinetic parameters of Berinert P in subjects with HAE either on prophylactic or on-demand therapy following IV administration

Parameters	Prophylactic (n = 15)	On-demand (n = 25)
AUC (U*h/mL) (15U/kg)	20.5 ± 19.1 (6.3-86.1)	20.0 ± 14.5 (2.9-69.7)
Clearance (mL/h/kg)	1.1 ± 0.6 (0.2-2.4)	1.2 ± 1.0 (0.2-5.2)
Vss (mL/kg)	39.5 ± 9.9 (24.1- 66.4)	51.4 ± 10.9 (23.3-69.2)
Half-life (hrs)	33.3 ± 19.8 (10.3-96.0)	43.9 ± 22.4 (7.9-90.4)
MRT (hrs)	48.0 ± 28.5 (14.9-138)	63.4 ± 32.3 (10.5-130.5)

Mean ± SD, numbers in parenthesis are range

In-vivo recovery (IVR):

IVR was assessed in two ways:

- The classical IVR, relating the absolute increase in C1INH level to the Berinert p dose, standardized to 1 U/mL volume of plasma
- The incremental IVR, relating the increase in C1INH and the Berinert p dose, standardized to 1 U/kg body weight

In both cases the increase in C1INH was defined as the difference between the maximum concentration of C1INH during 4 hours after start of drug administration and the baseline C1INH level before drug administration. The mean incremental IVR of Berinert P in all subjects, children, adults, patients on prophylactic therapy, and patients on demand therapy was 2.6 ± 1.1 , 2.2 ± 0.3 , 2.7 ± 1.1 , 3.2 ± 1.3 , and 2.3 ± 0.7 %/U per kg body weight, respectively. Mean IVR was higher for subjects on prophylactic treatment compared to subjects with on-demand treatment.

Comments

The sponsor fitted the plasma concentrations vs time data to a one-compartment model but a thorough examination of the data indicates that the concentrations vs time data can not be fitted to one compartment model. In fact, the nature of the data is such that the compartmental modeling for most of the subjects is not feasible. The following plots of concentrations vs time data will depict the difficulty of fitting the data to compartmental modeling. The plots (Figures 1 & 2) represent one or two-compartment modeling of plasma concentrations vs time data (subject #1). It is quite evident from the plots that even 2-compartment model is inadequate to describe the data. Therefore, a non-compartmental approach appears to be more appropriate than compartmental modeling.

Figure 1

Subject -b(6)- (1 compartment model) unadjusted

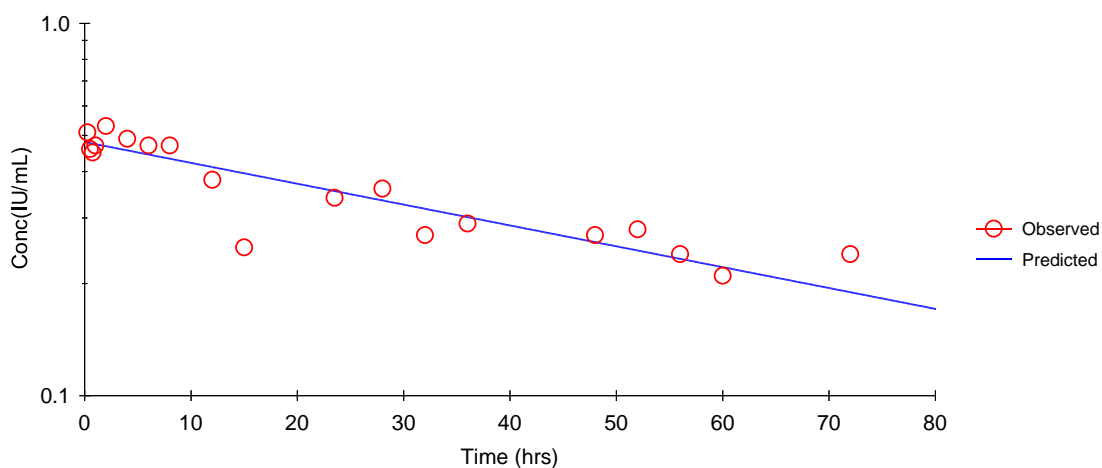
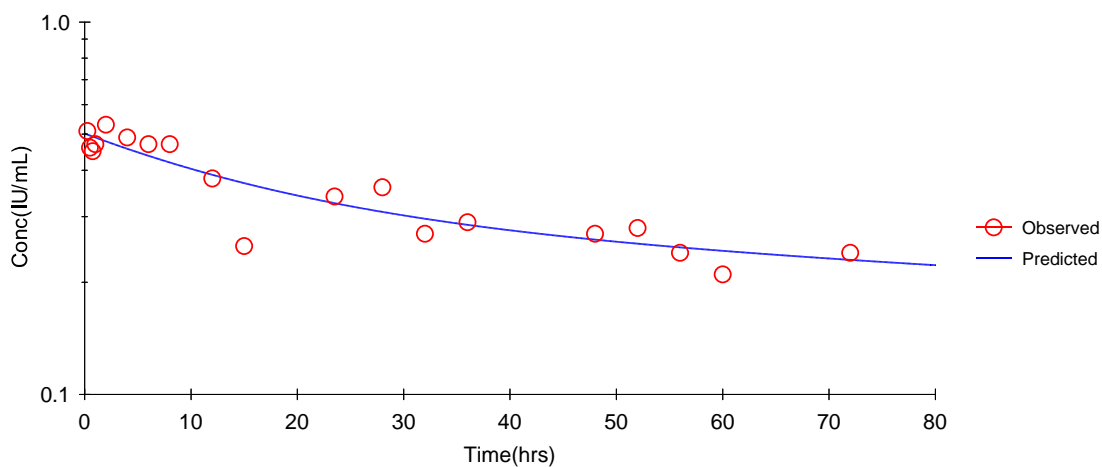


Figure 2

Subject -b(6)- (2 compartment model) unadjusted



Non-compartmental Analysis

Considering that a compartmental analysis for most of the subjects is not possible, the FDA requested the sponsor to re-analyze the data using non-compartmental approach. The FDA also requested the sponsor to analyze the data by the following approaches.

- With and without base line correction

- With and without extrapolation of the data (AUC from time zero to the last concentration or from time zero to infinity). This was done because the extrapolation added a substantial area to the tail portion of the AUC and area under the moment curve (AUMC).
- Half-life was estimated using the equation mean residence time (MRT)/1.44.

The sponsor complied with the FDA's request and submitted a reanalysis of the data using non-compartmental approach. The results of the analysis are summarized below.

TABLE 3
Pharmacokinetic parameters of Berinert P in subjects with HAE by non-compartmental analysis (adjusted for baseline (n=40))

Parameters	Extrapolated	Non-extrapolated
AUC _(0-inf) (hr x IU/mL)*	19.5 ± 17.4 (4.4-89.0)	Not applicable
AUC _(0-t) (hr x IU/mL)*	Not applicable	12.5 ± 6.5 (3.9-34.7)
CL (mL/hr/kg)	1.16 ± 0.67 (0.17-3.38)	1.49 ± 0.73 (0.43-3.85)
V _{ss} (mL/kg)	46.6 ± 12.9 (23.4-86.4)	35.8 ± 10.2 (14.1-56.1)
Half-life (hrs)	33.3 ± 22.0 (3.7-93.9)	18.1 ± 3.8 (7.4-22.8)
MRT (hrs)	53.1 ± 31.2 (16.4-139.2)	26.1 ± 5.4 (10.7-33.0)

*based on 15 U/kg dose

Mean ± SD, numbers in parenthesis are range

TABLE 4
Pharmacokinetic parameters of Berinert P in subjects with HAE by non-compartmental analysis (unadjusted for baseline (n=40))

Parameters	Extrapolated	Non-extrapolated
AUC _(0-inf) (hr x IU/mL)*	60.5 ± 34.2 (21.7-187.0)	Not applicable
AUC _(0-t) (hr x IU/mL)*	Not applicable	27.2 ± 8.2 (15.7-44.7)
CL (mL/hr/kg)	0.31 ± 0.14 (0.08-0.69)	0.60 ± 0.17 (0.34-0.96)
V _{ss} (mL/kg)	28.7 ± 7.3 (16.7-41.7)	18.7 ± 4.7 (11.1-27.6)
Half-life (hrs)	72.2 ± 33.2 (20.5-173.6)	21.9 ± 1.7 (16.5-24.4)
MRT (hrs)	108.1 ± 47.6 (39.4-253.6)	31.6 ± 2.4 (23.7-35.2)

* based on 15 U/kg dose

Mean ± SD, numbers in parenthesis are range

The extrapolation of the data resulted in a substantial addition of the area to the tail portion of AUC and AUMC. This in turn resulted in low clearance of berinert P. The half-life of berinert P was also fairly long. The mean half-life of berinert P was 72.2 hours (unadjusted for baseline and extrapolated) based on 72-hour blood sampling. Overall, PK parameters generated from both adjusted and unadjusted baseline values using extrapolation are mere numbers and not acceptable.

Comments

There are some serious conceptual and methodological problems with the sponsor's PK data analysis (both compartmental and non-compartmental analysis). These are as follows:

1. As mentioned earlier and demonstrated through compartmental analysis in this review that the nature of the data is such that a compartmental analysis is not possible for most of the subjects. It should also be noted that a compartmental analysis is not mandatory to estimate PK parameters of a compound. A non-compartmental approach can be taken.

2. Following the FDA request, the sponsor analyzed the data by non-compartmental approach using both baseline adjusted and unadjusted concentrations. The data were analyzed both from time 0 to infinity (extrapolated) and from time 0 to the last measurable concentration (non-extrapolated).

Baseline adjusted analysis:

The extrapolation of the data resulted in substantial addition to the total AUC and AUMC due to the large contribution from the tail. The FDA accepts only 20% area from the tail to the total AUC. The sponsor's extrapolated area for AUC and AUMC ranged from 1% to 142% (mean = 43%) and 3% to 999% (mean = 219%) of the total area, respectively. There are only 14 out of 40 subjects that have AUC tail portion less than 20%. The mean clearance and half-life in these 14 subjects were 1.76 ± 0.67 mL/hr/kg, and 14.24 ± 5.97 hours, respectively.

In order to appropriately estimate half-life of a drug, generally blood samples are taken for 4 to 5 half-lives. In some cases, where half-life is very long (several days or weeks) blood sampling for 3 half-lives can be accepted. For berinert P, blood samples were taken for 72 hours and if one accepts 3 half-lives for blood sampling then an acceptable half-life for berinert P will be 24 hours. The extrapolated half-life is more than 24 hours in 24 out of 40 subjects. The estimated half-lives in some subjects (n = 4) are even longer than 72 hours. The mean half-life for berinert P was 33.3 ± 22 hours (range: 3.7 to 93.9 hours). Overall, the estimated half-life of berinert P is not accurate and unacceptable mainly due to the difficulty in fitting the data.

When the half-life of berinert P was calculated indirectly from non-extrapolated MRT, the mean half-life of berinert P was 18.1 ± 3.8 hours (range: 7.4-22.8), which was reasonable from both mean and range perspective.

Baseline unadjusted analysis:

The sponsor's extrapolated area for AUC and AUMC ranged from 17% to 318% (mean = 114%) and 61% to 2962% (mean = 710%) of the total area, respectively. There was only 1 subject out of 40 that have AUC tail portion less than 20%. The extrapolated half-life is more than 24 hours in 39 out of 40 subjects. There were 17 subjects in which half-life was greater than

72 hours. The mean half-life for berinert P was 72.2 ± 33.2 hours (range: 20.5 to 173.6 hours). Overall, the estimated half-life of berinert P is not accurate and unacceptable.

When the half-life of berinert P was calculated indirectly from non-extrapolated MRT, the mean half-life of berinert P was 21.9 ± 1.7 hours (range: 16.5-24.4), which was reasonable from both mean and range perspective.

Overall, extrapolated PK data for Berinert P is not acceptable. Therefore, PK labeling will be derived from non-extrapolated data analysis (baseline adjusted and unadjusted).