Summary Basis for Regulatory Action

Date	11 December 2011
From	L. Ross Pierce, M.D., Committee Chair
Subject	Summary Basis for Regulatory Action
BLA Supplement#	STN 125287/110
Applicant	CSL Behring
Date of Submission	25 February 2011
PDUFA Goal Date	26 December 2011
Proprietary Name / Established (USAN) names	Berinert/ C1 Esterase Inhibitor (Human)
Proposed Indication(s)	**Treatment of acute laryngeal attacks of hereditary angioedema (HAE) in adult and adolescent patients.**
Recommended Action:	Approval (The original Berinert BLA was licensed for treatment of acute abdominal and facial attacks of hereditary angioedema (HAE) in adult and adolescent patients.**)**
Signatory Authorities Action:	**Approval** **Howard Chazin for Basil Golding_____** *Offices Signatory Authority:* *X I concur with the summary review* *□ I concur with the summary review and include a separate review or addendum to add further analysis* *□ I do not concur with the summary review and include a separate review or addendum*

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1. Introduction

This submission is a Biologics License Prior Approval Supplement (PAS) from CSL Behring (CSLB) to the Biologics License Application (BLA) for Berinert (C1 Esterase Inhibitor (Human) (STN 125287). Berinert is available in a lyophilized formulation, and has been licensed since 2009 for the following indication:

- *Treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients.*

At the time of original licensure, CSLB agreed as a post-marketing commitment (PMC #2), to complete and submit a final study report for its uncontrolled open label extension Phase 3-4 study CE 1145_3003. This study, entitled: "Open label extension study of CE1145 (Human pasteurized C1 esterase inhibitor concentrate) in subjects with congenital C1-INH deficiency and acute HAE attacks (follow-up of study no. CE1145_3001)", hereafter, **Impact 2 Study**, was an extension of the randomized, placebo-controlled IND pivotal trial CE1145_3001 that supported initial licensure. This PAS contains the final study report for the Impact 2 study in fulfillment of the above-described PMC and in support of the new indication for: **treatment of acute laryngeal edema attacks in adult and adolescent patients with hereditary angioedema due to C1-Esterase Inhibitor Deficiency**.

The PAS also contains a peer-reviewed publication from the medical literature describing a historical cohort of subjects with HAE who were not treated with C1-INH for laryngeal edema (LE) attacks (Konrad Bork, Sven-Erik Barnstedt. Treatment of 193 Episodes of Laryngeal Edema with C1 Inhibitor Concentrate in Subjects with Hereditary Angioedema. Archives of Internal Medicine 2001;161:714-718), hereafter **Bork paper**. The sponsor used data from this historical cohort to conduct a retrospective comparative analysis of the duration of acute laryngeal HAE attacks among subjects treated with Berinert in the Impact-2 study compared to the duration of acute laryngeal HAE attacks that were not treated with C1 esterase inhibitor (Human) (C1-INH). In addition, the same publication contains an analysis of the duration of LE HAE attacks in 8 subjects who received a related formulation of Berinert, Berinert HS, for some of their attacks and no treatment for some of their other attacks.

The application is not subject to the Pediatric Research Equity Act (PREA) because the product has Orphan Designation for the treatment of HAE attacks.

2. Background

C1-INH products represent replacement therapy for HAE patients with inadequate functional C1-INH levels and is aimed at aborting or preventing acute HAE attacks. When the CI-INH product is infused to treat an acute HAE attack that has already begun, it is called “treatment.” In contrast, routine prophylaxis therapy involves the administration of a C1-INH product at appropriate regular intervals in an attempt to prevent or greatly reduce the frequency of acute HAE attacks. Berinert was approved for the treatment of acute abdominal or facial HAE attacks, but is not approved for prophylaxis to prevent HAE attacks. Another plasma-derived C1-INH product, Cinryze, however, is approved for routine prophylaxis to reduce the frequency of acute HAE attacks, but is not approved for treatment of acute HAE attacks.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The original Berinert BLA was approved in 2009 (STN 125287).

Berinert is a lyophilized powder in single use vials containing the following nominal amount of C1 Esterase Inhibitor (Human): 500 U.

Each vial is labeled with the actual C1-INH activity expressed in Units (U) per vial. Biological potency is determined using an in vitro assay that employs an in-house C1-INH concentrate standard. One Unit of the standard is approximately equal to the level of C1-INH activity found in 1 mL of fresh citrated human plasma, which is equivalent to 270 mg/L or 2.5 microM/L.

The active component of the product is a purified single-chain glycoprotein consisting of 478 amino acid residues. The product is prepared from large pools of plasma from U.S. donors. The purification process includes 3 steps shown via *in vitro* spiking experiments to reduce the risk of viral transmission by the product. These steps are: heat treatment in aqueous solution at 60 degrees C x 10 hours, hydrophobic interaction chromatography, and nanofiltration using 20 nm and 15 nm filters in series.

Each vial of 500 U of C1-INH contains 50 to 80 mg of total protein and the following stabilizers in the listed mass ranges:

- Sodium Chloride 70 - 100 mg
- Glycine 85 – 115 mg
- Sodium Citrate 25 – 35 mg

The product contains no preservative.

Berinert is packaged with a 10 mL vial of Sterile Water for Injection, USP, and a Mix2Vial Filter needle-free Transfer Device.

Berinert should be stored at 2 – 25 deg. C in powder form.

b) CBER Lot Release

Section is not applicable for this efficacy supplement.

c) Facilities review/inspection

The product is manufactured at:

CSL Behring GmbH
Emil-von-Behring-Str. 76

35041 Marburg, Germany
FE1 # 3003098680

There are no ongoing or pending investigations or compliance actions with respect to the above facility or its products. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this submission.

4. Nonclinical Pharmacology/Toxicology

There were no new toxicology data submitted with this PAS. Toxicology studies in support of the initial Berinert approval were submitted under original BLA STN 125287.

5. Clinical Pharmacology

a) Mechanism of Action

C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors known as serpins. As with the other inhibitors in this group, C1 esterase inhibitor has an important inhibiting potential on several of the major cascade systems of the human body, including the complement system, the intrinsic coagulation (contact) system, the fibrinolytic system, and the coagulation cascade. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation and consumption of the C1 esterase inhibitor.

C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade.

HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system

activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.

Administration of Berinert to individuals with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein. The plasma concentration of C1 esterase inhibitor in healthy volunteers is approximately 270 mg/L.

b) Pharmacokinetics

The pharmacokinetics 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. All subjects received a single intravenous injection of Berinert ranging from 500 Units to 1500 Units. Blood samples were taken during an attack-free period at baseline and for up to 72 hours after drug administration. Pharmacokinetic parameters were estimated using non-compartmental analysis (with or without baseline adjustment). **Table 1** (below) summarizes the pharmacokinetic parameters in 35 adult subjects with HAE.

Table 1: Pharmacokinetic Parameters of Berinert in Adult 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)

AUC: Area under the curve
CL: Clearance
$V_{ss:}$ Volume steady state
MRT: Mean residence time
*Based on a 15 unit/kg dose. Numbers in parenthesis are the range.

Table 2 summarizes the pharmacokinetic parameters in 5 pediatric subjects (ages 6 through 13) with HAE. When adjusted for baseline values, the half-life of Berinert compared to adults was shorter and clearance (on a per kg basis) was faster in this limited cohort of children. The clinical implication of this difference is not known.

Table 2: Pharmacokinetic Parameters of Berinert in Pediatric Subjects 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)

AUC: Area under the curve
CL: Clearance
$V_{ss:}$ Volume steady state
MRT: Mean residence time
*Based on a 15 unit/kg dose. Numbers in parenthesis are the range.

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

6. Clinical/ Statistical

a) Clinical Program

In fulfillment of a PMC, CSLB completed and submitted the final study report for the Impact 2 study in this PAS. The objectives and design of the Impact 2 study, in conjunction with supportive data from the Bork paper, were considered adequate to support licensure of Berinert for the requested indication, treatment of laryngeal attacks, since the product is safe and effective at the same proposed dose for the treatment of acute abdominal HAE attacks. Both laryngeal and abdominal HAE attacks are submucosal in nature.

During product development for Berinert, CBER was prepared to accept a historical control due to the perceived difficulty of randomizing subjects to placebo with this condition (since it can be life-threatening). Although sponsors of other products being investigated for treatment of acute HAE attacks have conducted studies in which subjects with ------ b)(4)----------HAE attacks have been randomized to active or placebo arms in a masked fashion (with provision for open-label treatment with active product if there is a threat of significant airway compromise), CBER concluded that

it would be difficult to conduct an adequately powered placebo-controlled clinical trial of C1-INH in this population.

Summary of Extension Protocol No. CE1145_3003 (Impact 2)

Study Title: Open label extension study of CE1145 (Human pasteurized C1 esterase inhibitor concentrate) in subjects with congenital C1-INH deficiency and acute HAE attacks (follow-up of study no. CE1145_3001)

This prospective, open label, uncontrolled extension of a phase III, controlled trial was conducted in 15 multinational centers and was designed to enroll up to 60 subjects with C1-INH deficiency who had qualified for the pivotal trial CE1145_3001 and were now experiencing acute HAE attacks at any anatomical location. The duration of the extension protocol was 36 months, starting from the time when the last subject was enrolled or until product licensure, whichever came first. Subjects in the extension study (with Type I or II HAE) were administered a single dose of 20 U Berinert intravenously per attack. The primary endpoint was time to start of HAE symptom relief, a subjective endpoint, analyzed by a Wilcoxon rank test. The secondary efficacy endpoint was time from start of study medication administration to complete resolution of all HAE symptoms. The time between HAE attack onset and the time of Berinert administration also was recorded on the case report form, permitting calculation of the total duration of HAE attacks. Viral safety follow-up at 3 months was conducted.

Retrospective analyses of the efficacy and safety of CE1145 for treatment of *laryngeal attacks* was conducted and presented in an addendum to the study report. A Data Safety Monitoring Board (DSMB) monitored study safety. The primary analysis used the Intent-to-Treat (ITT) population.

The coordinating investigator for the Impact 2 study was Timothy Craig, D.O., Allergy & Respiratory Research, Penn State University, Hershey, Pennsylvania.

Study Inclusion Criteria:

- Prior eligibility for study CE1145_3001 (that had required the subject to have had an acute abdominal or facial HAE attack, which was treated under the earlier protocol CE1145_3003).
- An acute HAE attack at any anatomical location.

- Treatment with study medication in study CE1145_3001 more than 24 hours ago, except in the case of laryngeal edema.
- Written informed consent.

Study Exclusion Criteria:

- Life expectancy < 6 months
- Incurable malignancies with metastasis
- History of hypersensitivity to study medication
- Acquired angioedema due to C1-INH (e.g., onset at age > 40 yrs, no family history, no known HAE mutation, low C1q level in plasma)
- All types of angioedema other than HAE.
- End-stage liver disease (i.e., Child-Pugh score B or C)
- Pregnant, breast feeding, or with intentions to breast feed.
- Treatment with another investigational drug within past 30 days other than CE1145.
- Treatment with any C1-INH concentrates within the previous 24 hours.
- Treatment with angiotensin converting enzyme inhibitors within the previous 4 weeks.
- Treatment with fresh frozen plasma or native plasma within 7 days.
- [Use of] narcotic pain meds and/or anti-emetics between start of attack and administration of study medication.
- Evidence of narcotic seeking behavior and/or drug addiction (including ethanol abuse).

Additional Highlights of the Impact 2 Study Protocol

All HAE attacks [involving any body site] occurring after completion of the 24 hour evaluations in the pivotal study were eligible for retreatment with a single dose of 20 U/kg of Berinert C1-INH.

Determination of onset of time to initial and complete relief of HAE attack symptoms was to have been performed as in pivotal study CE1145_3001. Diaries were used to record time to total resolution of attack if the subject was discharged before the attack had completely resolved.

The investigator was to assess the time to initial relief of symptoms every 15 minutes x 2 hrs, then every 30 minutes x 2 hrs, then at hours 5, 6, 7, 8, 12,

16, 20, and 24 hours using the question, **"Taking into account all of the symptoms you experienced with this HAE attack, are you confident that it is starting to improve?** A "yes" answer would prompt the question, **"Have all symptoms of the HAE attack resolved completely?"**

The subject was asked to specify more precisely the exact time the pertinent endpoint (time to initial and complete resolution of HAE symptoms) was reached within the past time interval between assessment time points.

The primary endpoint was deemed to have been achieved if the answer to the question concerning initial improvement of symptoms was "yes" at 2 consecutive time points.

The study was uncontrolled and open label.

Subjects on prophylactic treatment with androgens, tranexamic acid, or aminocaproic acid were able to be included but the dosage of Berinert was to have been kept constant after the onset of an attack until it resolved completely.

Subject Disposition in the Impact 2 Study

The first subject enrolled 31 August 2005.
The last subject completed the study 26 February 2010.

The extension study was conducted at 14 U.S. sites and 1 Canadian site. Each site enrolled from 1 to 16 subjects. A total of 57 subjects were enrolled and treated for a total of 1085 attacks.

Only 18 subjects (32%) completed the study. Thirty-nine (68%) discontinued the study prematurely for the following reasons:

- Withdrawal of consent to participate in another study – 13 subjects
- Withdrawal of consent due to receiving prophylactic C1-INH treatment – 8 subjects.
- Withdrawal of consent (otherwise unexplained) – 1 subject
- Lost to follow-up – 13 subjects (23%).
- Prematurely discontinued due to an AE (infusion related reaction) – one subject.

- Withdrawal because genetic testing did not confirm HAE diagnosis – one subject.

The study had a large proportion of subjects (23%) lost to follow-up. At FDA request, the sponsor provided a summary of attempts to contact each subject lost to follow-up,

Demographics:

Females: 38 subjects (67%)

Males: 19 subjects (33%)

Mean age: 31.9 yrs

Age range 3 to < 12 years: 1 subject

Age range 12 to < 17 years: 6 subjects (10%)

Age range 17 to < 65 yrs: 87.7%

Caucasian: 87.7%

Black: 3 subjects (5.3%)

Oriental: 2 subjects (3.5%)

Hispanic: 1 subject

HAE Type I: 49 subjects (86%)

HAE Type II: 7 subjects (12%)

Mean body weight: 77.1 kg

Demographics of Impact-2 Subjects Treated with Berinert for LE HAE Attacks

Age range 12 - < 16: 2 subjects

Age range 12 - < 17: 3 subjects

Age range 17 – 53: 13 subjects

Size of Efficacy Datasets

The Intent to Treat (ITT) dataset included all 57 subjects and all 1085 attacks.

The Per Protocol (PP) dataset included 56 subjects and 1073 attacks (98.9%).

Table 3 below summarizes the percentage of HAE attacks and number of subjects experiencing the attacks by location.

Table 3: Location of HAE Attacks

Location	No. (%) of HAE Attacks	No. (%) of Subjects
Abdominal	51 (89.5%)	747 (68.8%)
Peripheral	235 (21.7%)	30 (52.6%)
Facial	51 (4.7%)	21 (36.8%)
Larygeal	48 (4.4%)	16 (28.1%)

In addition to those attacks noted in Table 3, three attacks were classified as "other" in location (inner cheek, scrotum, and midline buttocks).

Sixteen of the 48 laryngeal attacks occurred in a single subject (--(b)(6)---).

Results - Efficacy Analyses of the Impact 2 Study

Given that the extension study was open-label, analyses were descriptive in nature and performed on both per-subject and per-attack bases, with 2-sided 95% confidence intervals for median time to onset of HAE symptom relief and median time to complete resolution of HAE attack symptoms. Per subject analyses averaged individual attack times over all treated attacks for each subject.

Pre-specified Analyses (all HAE anatomical locations)

In the primary efficacy endpoint analysis of the ITT population (n = 57 subjects with 1085 HAE attacks – all anatomic locations), median time to onset of HAE attack (any location) symptom relief was 0.46 hours in the per-subjects analysis and 0.37 hours in the per-attack analysis.

The secondary efficacy endpoint, median time from time of administration of C1-INH to complete resolution of all HAE attack symptoms was 15.48 hours in the per-subject analysis and 14.28 hours in the per-attack analysis.

Sponsor's Additional Pre-specified Efficacy Endpoint Analyses

- Proportion of subjects with $\geq$ 1 attack (any location) taking > 4 hours until onset of symptom relief

  Result: Nine HAE attacks in 4 subjects had onset of symptom relief of > 4 hours (7 peripheral, 1 abdominal, and 1 facial attack).

- Proportion of attacks with a time to onset of symptom relief (any HAE attack location) of > 4 hours

  Result: 90.2%

Sponsor's Additional Post-hoc Efficacy Analyses.

Individual mean time to onset of relief following C1-INH treatment was < 1 hour in 93.0% of subjects.

Individual subject mean times to complete resolution of HAE attack symptoms were < 24 hours in 71.9% of subjects in the sponsor's analysis.

Table 4: Subgroup Analyses by HAE Anatomical Attack Location

HAE Attack Location	Median Time to Onset of HAE Symptom Relief (hours)	Median Time (Hours) to Complete Resolution of HAE Attack Symptoms
Laryngeal (LE)	0.25	8.38
Abdominal	0.32	10.45
Facial	0.40	23.48
Peripheral	0.50	28.33

Note that the median time to complete resolution of HAE attack symptoms, summarized in **Table 4** above, is not the same as total duration of HAE attack. Rather, the time elapsed between attack onset and treatment with Berinert, plus the time from treatment to complete resolution of HAE Attack symptoms defines the total duration of an HAE attack. It should be recognized that in some cases the time of onset of the attack may have been estimated.

There were no clinically relevant or consistent trends to suggest that study site, gender, age group, race/ethnicity, type of HAE, use of androgens, absolute C1-INH dose, number of preceding C1-INH infusions, or presence of anti-C1-INH antibodies affected observed efficacy of Berinert.

Acute Laryngeal HAE Attacks

Laryngeal attacks numbered 48 in 16 (28.1%) of 57 subjects and comprised 4.4% of all HAE attacks during the trial. This is a higher proportion of all HAE anatomical attack locations than estimated in the Bork paper in which it had been estimated that approximately 1 out of every 125 HAE attacks involve laryngeal edema. Those authors estimated from retrospective record reviews and interviews with subjects, their physicians and hospital staff, that the ratio of laryngeal edema to “skin swellings” (facial, truncal and peripheral) to abdominal HAE attacks was approximately 1:70:54. The authors suggested that subjects are likely to remember all their laryngeal attacks, whereas they may forget some of their attacks in other locations. If Bork and colleagues are correct regarding this bias, then this would raise the question as to whether some of the laryngeal edema attacks in the present

study might have been misclassified. While this may seem unlikely, it is possible that some HAE attacks limited to the mouth, tongue, and/or pharynx might have been classified as laryngeal attacks, particular since the list of LE attack symptoms listed in the protocol included dysphagia.

The laryngeal HAE attacks in the Impact 2 study were broken down into the following attack intensity classes, summarized in **Table 5** below:

Table 5: Baseline Laryngeal Attack Intensity in Impact 2 Study

Intensity Category	Number of Attacks	Percentage of Attacks
Mild	7	14.6
Moderate	21	43.8
Severe	20	41.7
All combined	48	100%

One may compare this laryngeal attack intensity data with the observed overall percentage of severe attacks among all HAE locations of 19.4% (210 severe out of a total of 1085 attacks).

Table 6 below compares retrospective results of the overall duration of LE attacks in subjects treated with Berinert in the Impact 2 trial compared to the overall duration of LE HAE attacks not treated with C1-INH as reported by in the Bork paper. (2001)

Table 6: Retrospective ITT Analysis of Laryngeal HAE Attack Overall Duration (Hours)

Cohort	Mean Duration	Standard Deviation	Median Duration	90% C.I.	Range
Treated (Impact 2) N = 16	16.56	14.95	10.52	10.01 – 23.12	3.50 – 51.67
Untreated (Bork 2001) N = 32	88.31	31.90	96.00	78.75 – 97.87	24.00 – 132.00

P < 0.00001 for difference in duration between comparison groups (2-sided, normal approximation**)**

In Impact 2, the median time elapsed from the start of laryngeal attacks to the time when Berinert was administered in the ITT population was 3.15 hours (range 0.85 to 94.5 hours).

The 2001 Bork paper does not describe how long it took for untreated subjects to come to medical attention after the onset of their laryngeal attacks.

Supportive Study of Treatment of LE Attacks with a Related Formulation of Berinert as published by Bork et al. (2001):

The Bork paper included a retrospective study in 8 subjects in which Bork compared the duration of LE HAE attacks for 19 such attacks that were not treated with C1-INH and for 18 such attacks treated with Berinert HS C1-INH (a total dose of 500 U initially, followed by an additional 500 U if the symptoms had not resolved after 30-60 min). A comparison of the durations of LE attacks between treated and untreated attacks appears in **Table 7** below. This data was reanalyzed from information in Table 2 in the Bork paper. (Table 2 from the Bork paper is not reproduced here.)

Table 7: FDA Analysis - Within-Subject Comparison (N = 8) of Overall Duration of LE HAE Attacks Treated with Berinert HS and Not treated with C1-INH

Cohort	Mean Number of LE Attacks per Subject	Mean[a] of Mean[b] LE Attack Durations for Each Subject	Median of Mean Durations for Each Subject	Range of Each Subject's Mean LE Attack Duration
Treated (Bork)	18	21.8	17.25	8 - 54
Untreated (Bork)	19	63.75	54	24 - 120

[a]Unweighted Mean
[b]Weighted Mean

Bork calculated the group mean values for LE attack duration differently from the FDA's calculations shown in the above table, obtaining a mean $\pm$ SD of 95.4 $\pm$ 32.1 hours for the untreated attacks and a mean $\pm$ SD of 14.5

± 9.7 hours for the treated attacks (p = 0.01). Despite this difference in analytical methodologies/outcomes, these within subject analyses lend support to the conclusion that Berinert is efficacious in substantially shortening the duration of LE HAE attacks.

Subgroup Analysis by Age – Adolescents (N=2)

Impact-2 Subject --(b)(6)--, age 15, had 4 LE attacks of 5.2, 4.42, 6.07, and 4.67 hours total duration after treatment with Berinert.

Impact-2 Subject ---(b)(6)----, age 13 had a single LE attack of 10 hours treated with Berinert.

Although the number of adolescent subjects age 12 - < 16 in Impact-2 was small (n = 2), the duration of their LE attacks following treatment with Berinert was consistent with the duration of LE attacks among all Berinert-treated Impact-2 subjects regardless of age (n = 16).

Protocol Violations/Deviations

Protocol Violations/Deviations included:

- Two subjects with a total of 3 attacks who had taken narcotic pain medication and/or anti-emetics between start of attack and administration of study medication;
- One subject for one attack who had taken C1-INH concentrate within 24 hours before the start of study medication;
- Three subjects who had 7 attacks for which they received < 75% of the protocol-specified dose of 20 U/kg;
- Two subjects for whom there had been evidence of narcotic-seeking behavior and/or drug addition; and
- One subject for whom genetic testing, performed retrospectively, did not confirm the diagnosis of HAE.

BIMO Inspections:

----------Information withheld per the Privacy Act----------.

1 page withheld per the Privacy Act.

Discussion of the Limitations of the Efficacy Data Supporting the Use of Berinert for the Treatment of Acute Laryngeal HAE Attacks

Generally, historically controlled analyses are subject to bias because there is less assurance that the test and control cohorts are comparable than is the case with a randomized, concurrently controlled study. Retrospective analyses are subject to more bias than prospective studies due to uncertainty in the methods used in collecting data. Before the sponsor performed the analysis of the duration of LE HAE attacks treated with Berinert vs. the duration of untreated LE HAE attacks, FDA communicated to the sponsor that it would accept a historical control (see Section 6a).

There are limitations to the supportive data from the retrospective within-subject comparison involving 8 subjects with LE attacks who were untreated for some attacks and treated with other attacks with Berinert HS, a formulation (heat treated in aqueous solution at 60 deg C x 10 hours) marketed in Germany and related to Berinert. It should be noted, that the Berinert dosage regimen used in the Bork paper overlapped with, but differed somewhat, from the dose of 20 U/kg used in the Impact 2 study.

An exact comparison of the similarity between the historical control group and the subjects treated for LE HAE in the Impact 2 study was not possible. An exact comparison was not possible because the sponsor contacted the author of the publication from which the historical control data were taken and individual demographic and baseline characteristics for each subject comprising the historical control were no longer available. Nevertheless, the sponsor was able to compare the sex, mean and range for age, and HAE Type between subjects in Impact 2 and a subset of 24 of the 32 untreated historical control subjects, as well as with a different group of 18 subjects, 8 of whom were included in the untreated historical control cohort. The subjects treated for LE attacks in the Impact 2 were somewhat younger than those in the Bork paper. In both the Impact 2 study and the Bork paper the majority of subjects with LE attacks were female and were HAE Type 1 subjects.

There were differences in the precision of estimates of acute LE HAE attack duration between the Impact 2 study and the Bork paper historical control subjects. Duration of individual LE attacks recorded in the Impact 2 study are presented with more precision (up to 2 decimal places). In contrast, duration for untreated LE HAE attacks from historical controls in the Bork

paper were listed in even multiples of 24 hours. Much of Bork's historical data may likely have been retrospectively collected, so this may contribute to some bias in the comparative analysis.

Total attack duration for both the Impact 2 study and the historical control are only estimates, because subjects are not, in most cases, under direct observation by a health care professional at the time the attack commences. Thus, the data are dependent on the statements of subjects for the time of onset for each LE attack.

The durations of individual LE HAE attacks for subjects never treated with C1-INH are not provided in the Bork paper, yet they appear in the sponsor's data listing (Appendix 8.2, Listing C1H16.2.2). The sponsor confirmed that individual attack duration was not available for the historical controls, so the data submitted by the sponsor for individual attack duration were generated by the sponsor by repeating the within-subject mean attack duration provided by Bork. This presentation of data by the sponsor was misleading. However, the statistical analyses performed by the sponsor and by FDA to compare LE HAE attack duration between the subset of Impact 2 subjects treated with Berinert for LE attacks and the Bork historical control subjects utilized mean LE attack duration for each subject, not individual LE attack durations. As a result, this presentation of the historical cohort data did not bias the sponsor's efficacy analysis, given the methodology used. In a teleconference held on 16 December 2011, the sponsor was asked to explain their presentation in the BLA supplement of individual LE attack duration for the Bork historical control cohort when, according to the sponsor, Bork had not recorded durations of individual HAE attacks for the historical control. The sponsor confirmed that, for 30 of 32 Bork paper historical control subjects not treated with C1-INH for LE HAE attack, only mean durations of LE HAE attacks were available and not durations of individual LE HAE attacks.

One subject (#2) in the 2001 Bork paper was reported to have a total of exactly 200 LE HAE attacks, of which exactly 100 were untreated and exactly 100 were treated with C1-INH. The duration of the untreated LE attacks for this subject are given as exactly 96 hours for 25 attacks and as exactly 120 hours for 75 attacks. This distribution of LE HAE attack duration does not show an expected degree of biological variation, even if the values were rounded to the nearer 24 hour duration. This subject's data were discarded by the same author for several of the key analyses in a 2003

Bork paper (Bork K, Hardt J, Schincketanz K-H, Ressel. Clinical Studies of Sudden Upper Airway Obstruction in Subjects with Hereditary Angioedema Due to C1 Esterase Inhibitor Deficiency. Arch Intern Med 2003:163:1229-1235) "because such an extreme number of episodes of laryngeal edema has not been previously reported in the literature." Nevertheless, the paper states, "One subject had ***approximately*** [emphasisadded] 200 episodes of laryngeal edema, which was confirmed by his general practitioner and the hospital he attended."

Efficacy Conclusion:

Despite the limitations of the efficacy data as described above, the sponsor has shown that the use of Berinert for LE HAE attacks shortens the median time to onset of symptom relief and median time from time of administration of C1-INH to complete resolution of all HAE attack symptoms. The retrospective comparative ITT analysis shows significant improvement in mean duration of LE attack.

Given the large difference (approximately 72 hours, $P < 0.00001$) in mean total duration of acute laryngeal HAE attacks between untreated LE attacks as reported for 32 subjects in the 2001 Bork paper (324 LE attacks) and 16 subjects in the sponsor's Impact-2 study (48 LE attacks), *it appears unlikely that this difference could be largely or completely explained by the various biases discussed which are inherent in a retrospective analysis of a recent study and a much older historical control*. It is doubtful that differences in ancillary concomitant therapy alone could have produced the reported difference in duration of treated and untreated acute LE HAE attacks.

Very substantial and clinically significant differences in favor of Berinert were observed for both the between-subject comparison of LE HAE attack duration among subjects experiencing LE attacks during the Impact 2 study compared to the Bork historical control, as well as the between-subject comparison of untreated and Berinert HS-treated LE attacks as published by Bork. Both analyses were statistically significant.

7. Safety

The safety of Berinert 20 U/kg for the treatment of acute abdominal and facial HAE attacks in adults and adolescents was demonstrated in pivotal study CE1145_3001 prior to the original BLA licensure. The data presented from the Impact 2 study do not reveal new safety signals of concern for expanding the indication to include treatment of acute laryngeal HAE attacks.

Safety monitoring in the Impact 2 study included physical examination at baseline and at 24 hours or discharge if before 24 hours; vital signs at baseline, then every 1 hour until 4 hours after administration of Berinert, then every 4 hours until 24 hours or discharge; routine hematology, serum chemistries, viral studies, and immunogenicity; and CBC with differential and platelets.

Chemistries including electrolytes, Ca, total bilirubin, total protein, serum creatinine, urea, ALT, AST, GGT, LDH, CRP, and uinalysis were added in protocol amendment 3 and were to have been performed on day 1 before study medication, day 1-30, every 6 months, and at study end. Antibodies to C1-INH measured by central lab were added in protocol amendment 3 at baseline and q 3 months until end of study. If the baseline antibody result was positive at the 1st attack, the screening sample from pivotal study CE1145_3001 was to have been tested. Viral studies in conjunction with 1st attack only at baseline and at day 7-9 (PCR Parvovirus B19 only) and week 12. The week 12 adverse event (AE) assessment captured only serious adverse events (SAEs).

SAFETY RESULTS –

Adverse Events (AEs)

Deaths: none

Serious AEs (SAEs): 2 in 1 subject (HAE, staphylococcal infection, both considered unrelated to study medication, both resolved without sequelae.)

Discontinuation due to AE: 1 subject was discontinued due to an infusion-related reaction considered at least possibly related to study medication.

Twenty-five (44%) out of 57 subjects had 1 or more AEs.

The most frequently reported AEs in the per-subject analysis were headache (5 subjects, 8.8%) and nasopharyngitis (3 subjects, 5.3%). All other AEs occurred with a frequency of ≤ 3.5% each (≤ 2 subjects).

Fifty-nine (5.4%) of attacks were associated with 1 or more AE.

The most frequently reported AEs in the HAE attack analysis were headache and abdominal pain (8 attacks, 0.7% each) plus nausea (7 attacks, 0.6%). All other AEs occurred in 5 or fewer attacks (≥ 0.5% of attacks).

Eight (14%) subjects reported 1 or more AEs (a total of 11 attacks) that were classified as severe in intensity:

- Abdominal discomfort
- Abdominal tenderness
- Dry mouth
- Nausea
- Infusion related reaction
- Pharyngitis (streptoccal)
- Staphyloccal infection
- UTI
- Viral infection
- Muscle strain
- headache

Possibly-related AEs according to investigator assessment
(8 subjects (14%), 9 AEs):

- Influenza-like illness (2 AEs)
- Abdominal discomfort
- Dizziness
- Dry mouth
- Erythema infectiosum
- Headache
- Infusion related reaction
- Pruritis
- Rash

Laboratory AEs identified by investigators: 3 subjects

- Decreased K+ of 3.2 mmol/L in one subject
- Increased ALT of 94 U/L in one subject
- Increased AST of 114 U/L in the same subject having the above ALT elevation
- Urinary leucocytes and bacteria in one subject

The above abnormalities normalized or returned to non-clinically significant levels in each case.

Vital Signs: no clinically relevant changes

Physical Examinations: no safety signals

Viral Safety:

No product-related transmissions of HIV 1-2, HAV, HBV, HCV, or parvovirus B19 were observed.

Anti-C1-INH Antibodies:

Treatment-emergent positive anti-C1-INH antibodies were detected in 11 subjects. Another 8 subjects were positive at baseline screening for the prior pivotal study (CE1145_3001). Among the 19 total subjects who were antibody positive, the result was confirmed by isotyping in 15 subjects. No inhibitory antibodies were detected.

Comment on Safety of Berinert in Adolescents

The safety of Berinert in the proposed dose of 20 U/kg for adolescents for LE attacks already was established from data in the original BLA.

Postmarketing Experience

Berinert has been approved in the U.S. since 2009. Postmarketing adverse events in the FDA AERs database were recently reviewed for approved Berinert labeling supplement 117, which strengthened statements in the package insert concerning thrombotic and thromboembolic events to indicate that such events [in very small numbers] have been observed after

administration of Berinert at the recommended dose for the treatment of acute HAE attacks.

FDA concluded that recently examined postmarketing AERs database for Berinert does not change the favorable risk: benefit balance for the two existing indications or the new indication, treatment of acute laryngeal HAE attacks, for any age group.

Safety Conclusion:

The overall safety profile of Berinert is acceptable for adding the new indication for treatment of acute laryngeal HAE attacks. Safety is supported by results from the Impact 2 study, the pivotal study reviewed in the original BLA, and by postmarketing experience. No pattern of unusual safety signals was evident among the pediatric study population. The benefits of treatment with Berinert at 20 U/kg clearly outweigh the risks for the studied age populations.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this PAS.

10. Labeling

Prescribing Information (PI): APLB and the medical reviewer from the Clinical Review Branch, HFM-392 reviewed the draft package insert (PI) submitted by the sponsor. Comments from a promotional and comprehension perspective were provided to OBRR from APLB. FDA comments regarding the draft PI were sent to the sponsor. The sponsor subsequently submitted a revised PI. The sponsor ultimately accepted all of FDA's comments and recommendations regarding the draft PI with only minor modification.

Carton and immediate container labels: no changes to previously approved versions.

Patient labeling: Patient information is appropriately provided following the Package Insert's Full Prescribing Information.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends the approval of this supplement.

b) Risk/ Benefit Assessment

Efficacy and safety data were found adequate to make a favorable decision concerning potential benefit/ risk balance. Results from the Impact 2 clinical trial, in conjunction with published literature by Bork together with safety data from the prior pivotal IND study reviewed in the original BLA and a recent review of postmarketing data, support the new indication for treatment of acute laryngeal HAE attacks in adults and adolescents.

Given that acute laryngeal edema HAE attacks have been associated with a number of fatalities from asphyxiation (according to Bork, approximately 2% of LE HAE attacks require acute management with cricothyrotomy or tracheostomy), and given the safety and efficacy data for use of Berinert in the treatment of acute LE HAE attacks presented in this supplement, benefits appear to outweigh risks for the proposed new indication, treatment of acute laryngeal edema attacks in adult and adolescent patients with hereditary angioedema due to C1-Esterase Inhibitor Deficiency.

c) Recommendation for Post-Marketing Activities

Pharmacovigilance will continue through passive reporting and through active surveillance via the Berinert Registry, which have been ongoing since approval of the original BLA. The sponsor has agreed to intensify efforts encouraging participation in the Berinert Registry. It has also agreed to modify the Registry CRF to include information about prescription for and use of the product outside the clinic or hospital setting involving self-infusion by the patient/subject or another non-healthcare provider. In addition, the frequency of reporting on the status of the Berinert Register will be increased from annually to quarterly.

d) Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments related to this new indication.