# Summary Basis for Regulatory Action

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| **Date** | Thursday, October 8, 2009 |
| **From** | Felice D'Agnillo, Committee Chair |
| **Subject** | Summary Basis for Regulatory Action |
| **BLA #**<br>**Supplement#** | STN 125287/0 |
| **Applicant** | CSL Behring |
| **Date of Submission** | March 7, 2008 |
| **PDUFA Goal Date** | October 9, 2009 |
| **Proprietary Name / Established (USAN) names** | BERINERT / C1 esterase inhibitor (Human) |
| **Dosage forms** | 500 Units (U) per glass vial, Lyophilized |
| **Proposed Indication(s)** | Treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients. |
| **Recommended Action:** | Approval |
| **Signatory Authority(ies) Action** | **Basil Golding**_____<br>*Offices Signatory Authority:*<br>☐ *I concur with the summary review*<br>☐ *I concur with the summary review and include a separate review or addendum to add further analysis*<br>☐ *I do not concur with the summary review and include a separate review or addendum* |

| **Material Reviewed/ Consulted SBRA** | **List of specific documentation used in compiling** |
|---|---|
| Clinical Review | Ross Pierce |
| Statistical Review | Xue (Mary) Lin and Chinying (Jean) Wang |
| Clinical Pharmacology | Iftekhar Mahmood |
| Pharmacology/ Toxicology Review | Paul Buehler |
| CMC Review/Facilities | Felice D'Agnillo, Elena Karnaukhova, Omer I. Butt, Mahmood Farshid, Marion Michaelis, and J. David Doleski |
| Establishment Inspection Report | J. David Doleski, Marion Michaelis, and Felice D'Agnillo |
| Biomonitoring Review | Bhanu Kannan |
| Labeling | Jean Makie |
| Pharmacovigilance | Faith Barash |
| Advisory Committee Transcript | Not presented at BPAC |

## 1. Introduction

BERINERT is a purified, pasteurized, lyophilized preparation of human plasma-derived C1 esterase inhibitor derived from U.S. Source Plasma. The manufacturing process steps include --b(4)----, precipitation, --b(4)-------, heat treatment, and chromatography steps. BERINERT is supplied as a lyophilized powder in single-use glass vials. BERINERT is administered by intravenous injection after reconstitution with the appropriate volume of Sterile Water for Injection (USP) (supplied in the package). BERINERT is indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE), a disease characterized by low levels of endogenous or functional C1 esterase inhibitor.

## 2. Background

This original Biologics License Application (BLA) from CSL Behring for C1-esterase inhibitor (human) or BERINERT, indicated for the treatment of acute abdominal or facial attacks of HAE in adult and adolescent patients, was received in CBER/DCC on March 7, 2008 (STN#125287/0). The offices for CSL Behring are located in King of Prussia, PA, and the manufacturing facilities are located in Marburg, Germany. Orphan drug status was granted on October 16, 1992. The BLA submission qualified for priority review with an action due date of September 5, 2008. CSL Behring submitted an amendment on June 20, 2008, within 3 months of this action due date, that was classified as a Major Amendment and extended the review clock by 3 months.

On the action due date of December 5, 2008, FDA issued a Complete Response (CR) letter to the sponsor because of missing data from the pivotal trial datasets concerning confounding concomitant medications and the need to validate an additional manufacturing step for its viral reduction capacity. The sponsor responses to the CR letter were received by CBER on April 10, 2009. The submission was classified as a Class II response with a review deadline of October 9, 2009. Referral to the Blood Products Advisory Committee (BPAC) prior to licensure was not recommended (See Section 8).

C1 esterase inhibitor regulates the activation of complement, contact, and fibrinolytic systems. BERINERT is a purified, pasteurized, lyophilized preparation of human plasma-derived C1 esterase inhibitor derived from U.S. Source Plasma. The manufacturing process steps include --b(4)-------, precipitation, --b(4)-------, heat treatment, and chromatography steps. Viral clearance capacity of the manufacturing process has been demonstrated by validation studies on the pasteurization step, hydrophobic interaction chromatography, and a combination of steps involving chromatography and ammonium sulfate precipitation. BERINERT is supplied in single-use glass vials and is administered by intravenous injection after reconstitution with the appropriate volume of Sterile Water for Injection (USP).

The clinical studies for this BLA were conducted under IND--b(4)----. The BLA contains safety and efficacy data from one phase 3 trial that evaluated BERINERT for treatment of

single acute abdominal and facial attacks in patients with HAE (CE1145_3001). The primary efficacy endpoint of the study was self-reported time to the start of relief of HAE attack symptoms. A number of secondary and exploratory efficacy endpoints were also evaluated. Data are also provided from an unscheduled interim analysis of ongoing uncontrolled extension trial (CE1145_3003), designed to evaluate BERINERT for repeated dose safety and for treatment of acute attacks in patients with HAE attacks from any attack location. Interim safety data from the open-label extension study included assessments of immunogenicity (anti-C1 Esterase Inhibitor antibody formation), routine laboratory safety data, vital signs, and adverse events.

**3. Chemistry, Manufacturing and Controls (CMC)**

**General Manufacturing Summary:**

BERINERT or C1 esterase inhibitor (human) is manufactured from US Source Plasma by a series --b(4)-------, precipitation, --b(4)------, heat treatment, and chromatography steps. The composition of each vial of BERINERT is as follows: 500 U C1 inhibitor, 50-80 mg total protein, 85-115 mg glycine, 25-35 mg sodium chloride, and 70-100 mg sodium citrate. The product package consists of one carton containing a single-use vial of BERINERT and one 10 mL vial sterile water for injection (USP), and an additional carton with a Mix2Vial filter transfer set, a disposable 10 mL syringe, infusion set, and two alcohol swabs.

**Manufacturing Overview:**

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Additional Manufacturing Issues Addressed During Review Cycle:

i. The sponsor accepted the FDA recommendation to change the specification for Parvovirus B19 in the fractionation pool from a value of $10^5$ logs to $10^4$ logs.

ii. The sponsor accepted the FDA recommendation to implement -----b(4)----------
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iii. The sponsor accepted the FDA recommendation to implement alerts limits for ammonium sulfate concentration to better control the ---------b(4)----------
chromatography step.

**Drug Product Composition**

| Ingredient | Amount | Function of ingredient |
|---|---|---|
| C1 esterase inhibitor (U/mL) | --b(4)------- | Active ingredient |
| --b(4)---- citrate (mg/mL) | 2.5 - 3.5 | ---b(4)----- |
| Sodium Chloride (mg/mL) | 7 - 10 | ---b(4)----- |
| Glycine (mg/mL) | 8.5 - 11.5 | ---b(4)----- |

**Drug Product Release Specifications**

| Test | Specification |
|---|---|
| Dissolution time (min) | -b(4)- |
| Appearance | Colorless and clear solution |
| -----b(4)---------- | --b(4)------ |
| ------b(4)---------- | --b(4)------ |
| ------b(4)---------- | ---------b(4)---------- |
| Protein concentration (mg/mL) | --b(4)-- |
| Sodium citrate (mg/mL) | 2.5 - 3.5 |
| Glycine (mg/mL) | 8.5 - 11.5 |
| Sodium chloride (mg/mL) | 7 - 10 |
| Residual Moisture (%) | -b(4)-- |
| pH value | --b(4)---- |
| Purity (C1INH) (%) | -b(4)- |
| ----------b(4)---------- | ---b(4)----- |
| ----b(4)---------- | -b(4)-- |
| Pyrogens | Pharm. Eur./ CFR/USP |
| Sterility | Pharm. Eur./ CFR/USP |
| General Safety Test | CFR/USP |

**Validation of the Viral Clearance Capacity of the Manufacturing Process**

The manufacturing process for BERINERT includes steps designed to reduce the risk of viral transmission. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and plasma preparation. Each individual plasma donation used in the manufacture of BERINERT is collected at FDA-approved blood establishments and is tested by FDA licensed serological tests for Hepatitis B Surface Antigen (HBsAg), and for antibodies to Human Immunodeficiency Virus (HIV-1/HIV-2) and Hepatitis C Virus (HCV). All plasma is tested by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1 and found to be nonreactive (negative). Manufacturing plasma pools are also tested for B19 DNA by NAT to ensure that the level in the pool does not exceed $10^4$ IU/mL.

The BLA provided validation data supporting the viral clearance capacity of two steps in the manufacturing process; pasteurization and hydrophobic interaction chromatography (HIC). The combined effect of pasteurization and HIC chromatography provided acceptable degree of clearance for the panel of viruses tested by the sponsor. However, the data pointed to unexpected heat stability of HIV and PRV in the pasteurization step under the manufacturing conditions. Based on these findings and the inherent limitations associated with hydrophobic interaction chromatography, FDA asked in the CR letter that the sponsor validate additional manufacturing steps for their capacity to clear HIV and PRV.

In response to the CR letter, the sponsor provided validation data for DEAE-Sephadex A50 Chromatography, QAE-Sephadex Chromatography and Ammonium Sulphate Precipitations steps in the manufacturing process for their combined capacity to clear HIV and PRV. These manufacturing steps were studied separately (as a single step) to determine their individual contribution to clearance of HIV and PRV. Validation data demonstrated that these manufacturing steps contribute to the removal of HIV and more significantly to the removal of PRV. The sponsor also provided a post-approval commitment to ----------b(4)----------

The table below demonstrates the total viral clearance in the manufacturing process of BERINERT including clearance data submitted for HIV-1 and PRV in response to the CR letter.

| Virus | Pasteurization | HIC | DEAE-Sephadex A50 chromatography QAE-Sephadex chromatography Ammonium Sulfate | Total Log Reduction |
|---|---|---|---|---|

| | | | Precipitation | |
|---|---|---|---|---|
| HIV | ≥ 6.6 | ≥ 4.5 | 4.3 | ≥ 15.4 |
| BVDV | ≥ 9.2 | ≥ 4.6 | | ≥ 13.8 |
| PRV | 6.3 | ≥ 6.5 | ≥ 7.7 | ≥ 20.5 |
| HAV | ≥ 6.4 | 4.5 | | ≥ 10.9 |
| CPV | 1.4 | ≥ 6.1 | | 7.5 |
| WNV | ≥ 7.0 | Not done | | N/A |

**Stability Testing**

Regarding the stability of the final bulk solution, the data provided in the submission support a maximum storage time of --b(4)-- when stored at ----b(4)---------- containers.

The long-term stability of BERINERT was evaluated using three lots of product stored at 2 – 8 °C and 25 °C. Accelerated stability data at ---b(4)---------- were also provided. Based on the review of the submitted data, a dating period of 30 months at a storage temperature of 2 to 25 °C is recommended. Stability data on the reconstituted product support a storage time not to exceed 8 hours when stored at 2 to 25 °C.

The sponsor will perform routine stability testing on -b(4)- of BERINERT per year. The stability protocol will include the following tests; ----------b(4)----------

The CMC review team finds that sufficient data and information have been provided on the chemistry, manufacture and controls to support licensure of BERINERT.

**CBER Lot Release**

CBER will release lots of BERINERT based upon review of results of in process and final release tests performed by the manufacturer and submitted in the Lot Release Protocols. Lot Release Protocols were reviewed and approved by CBER.

**Facilities**

BERINERT is manufactured by CSL Behring in Marburg, Germany.

CSL Behring GmbH, Emil-von-Behring-Straße 76, 35041 Marburg, Germany.

CBER conducted the pre-approval inspection of the Marburg facility from May 26 to June 3, 2008. During this inspection, CSL Behring was cited for fourteen FDA 483 items related to manufacturing and quality issues. The responses to the FDA 483 items were received, reviewed and found to be acceptable.

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

The primary facilities reviewer considers this submission approvable on the basis of the facilities information provided.

# 4. Nonclinical Pharmacology/Toxicology

Acute toxicity (i.v.) of BERINERT was performed in mice at 1500, 3000, and 6000 U/kg in rats at 1000, 2000, and 3000 U/kg. BERINERT demonstrated an acceptable toxicity profile at the highest acute dose administered. Repeat dose toxicity was studied over 14-days of dosing (20, 60, and 200 U/kg/day). Repeat dosing in the rat resulted in a neutralizing antibody response against C1 esterase inhibitor prior to completion of the study; therefore a full assessment of cumulative (14 day) toxicity in animals was inconclusive. Safety pharmacology of BERINERT administered to beagle dogs at a cumulative dose of 3500 U/kg demonstrated minimal effects on the cardiovascular and respiratory system. There was a dose dependent decrease in body temperature, reduced coagulation time, and a decreased in thrombocyte aggregation at multi-fold greater than the clinically recommended dose. Local tolerance (s.c.) of BERINERT was evaluated in rabbits at 25 and 75 U/kg. Injection site edema and histopathological changes were not observed over a 24 hour time period post dosing. No pathological signs were noted during necropsy.

Thrombotic events have been reported in association with C1 esterase inhibitor products when used off-label and at higher than labeled doses[1]. Animal models of thrombogenicity have confirmed micro-thrombi formation in normal animals following intravenous administration of C1 esterase inhibitor products at doses exceeding those indicated for plasma replacement in humans[2].

1. German Medical Profession's Drugs Committee. Severe thrombus formation of Berinert® HS. *Deutsches Ärzteblatt*. 2000;97:B-864.

2. Horstick, G *et al,* 2002. Application of C1-Esterase Inhibitor During Reperfusion of Ischemic Myocardium: Dose-Related Beneficial Versus Detrimental Effects *Circulation* 104:3125-3131.

# 5. Clinical Pharmacology

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 half-life and clearance (unadjusted for baseline) of BERINERT in 35 adults were 21.9 ± 1.7 hours and 0.60 ± 0.17 mL/hr/kg, respectively. The half-life and clearance (after adjusting for baseline) of BERINERT in 35 adults were 18.4 ± 3.5 hours and 1.44 ± 0.67 mL/hr/kg, respectively.

The half-life and clearance (unadjusted for baseline) of BERINERT in 5 pediatric patients (6-13 years) were 22.4 ± 1.6 hours and 0.62 ± 0.17 mL/hr/kg, respectively. The half-life and clearance (after adjusting for baseline) of BERINERT in 5 pediatric patients were 16.7 ± 5.8 hours and 1.9 ± 1.1 mL/hr/kg, respectively. 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 these differences is not known.

In-vivo recovery (IVR) was defined as the difference between the maximum concentration of C1 esterase inhibitor during 4 hours after start of drug administration and the baseline C1 esterase inhibitor level before drug administration. The mean incremental IVR of BERINERT 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.

## 6. Clinical/Statistical-Efficacy

The clinical portion of the submission consists of the final results of the phase 3 Hereditary Angioedema (HAE) double-masked, placebo-controlled dose-ranging multinational study protocol CE1145_3001 and results from an unscheduled interim analysis of the randomized controlled trial's (RCT's) open-label extension study CE1145_3003, the later being conducted only in the U.S at 10 centers. There are also foreign data for several small clinical trials in various indications and a retrospective data collection in pregnant HAE patients, plus foreign postmarketing surveillance data.

The safety and efficacy of BERINERT in the treatment of acute abdominal or facial attacks in subjects with hereditary angioedema were demonstrated in a placebo-controlled, double-blind, prospective, multinational, randomized, parallel-group, dose-finding, three-arm, clinical study - referred to as the randomized clinical trial (RCT). The RCT assessed the efficacy and safety of BERINERT in 124 adult and pediatric subjects with C1 Esterase Inhibitor deficiency who were experiencing an acute moderate to severe attack of abdominal or facial HAE. Subjects ranged in age from six to 72 years of age; 67.7% were female and 32.3% were male; and approximately 90% were Caucasian.

The study objectives were to evaluate whether BERINERT shortens the time to onset of relief of symptoms of an abdominal or facial attack compared to placebo and to compare the efficacy of two different doses of BERINERT. The time to onset of relief of symptoms was determined by the subject's response to a standard question posed at appropriate time intervals for as long as 24 hours after start of treatment taking into account all single HAE symptoms. In addition the severity of the single HAE symptoms were assessed over time.

Subjects were randomized to receive a single 10 unit/kg body weight dose of BERINERT (39 subjects), a single 20 unit/kg dose of BERINERT (43 subjects), or a single dose of placebo (42 subjects) by slow intravenous infusion (recommended to be given at a rate of approximately 4 mL per minute) within 5 hours of an attack. At least 70% of the subjects in each treatment group were required to be experiencing an abdominal attack.

The sponsor concludes that the phase 3 RCT "IMPACT I" study met its primary and both secondary endpoints for the high dose treatment arm (20 U/kg). FDA concurs, but, as noted below, found different p values than those the sponsor reported due to misclassifications by the sponsor of some subjects for whom 24 hour "poor/failure" values for the primary endpoint were to have been imputed, due to use of confounding concomitant medications that were "non-permitted" or "discouraged" by the protocol." "Discouraged" medications consisted of narcotic and non-narcotic analgesics and drugs with anti-emetic properties. The use of narcotic analgesics or anti-emetics starting at the time of onset of the HAE attack was an exclusion criterion for participation in the protocol. Their use was discouraged until 4 hours after study test drug was administered, at which point subjects could receive such medications and/or blinded rescue C1 Esterase Inhibitor or placebo. For rescue therapy, blinded placebo was administered if the subject originally received 20 U/kg of C1 Esterase Inhibitor, 20 U C1 Esterase Inhibitor was given if the subject was originally randomized to placebo, and another blinded 10 U/kg dose of active study product was administered if the subject had been randomized to receive 10 U/kg dose of active study product.

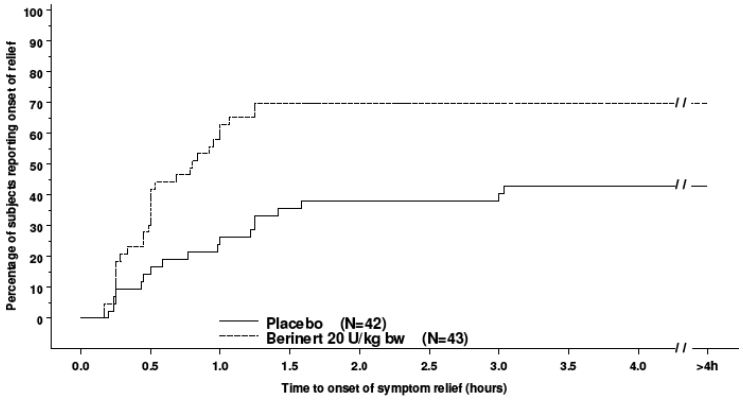
A dose-response effect was also seen for the primary and secondary endpoints, although a comparison of the low dose arm (10 U/kg) with placebo did not achieve statistical significance. This has led to a change in the recommended dose in Europe where this product has been used in an initial starting dose of 10 U/kg for acute HAE attacks for several decades.

The median time to onset of relief from symptoms of an HAE attack was 50 minutes for BERINERT 20 units/kg body weight, as compared to >4hours for placebo. The time to onset of relief from symptoms of an HAE attack for subjects in the 10 unit/kg dose of BERINERT was not statistically significantly different from that of subjects in the placebo group.

The figure below is a Kaplan-Meier curve showing the percentage of subjects reporting onset of relief of HAE attack symptoms as a function of time. Individual time points

beyond 4 hours are not presented on the graph, because the protocol permitted blinded rescue medication, analgesics, and/or anti-emetics to be administered starting 4 hours after randomized blinded study medication had been administered.

**Time to Onset of Symptom Relief with Imputation to > 4 Hours for Subjects Who Received any Rescue Medication* or Non-narcotic Analgesics Before Start of Relief**




**Rescue study medication with C1-INH, analgesics, anti-emetics, open-label C1-INH, androgens at increased dose, or fresh frozen plasma. Anti-emetics included antidopaminergics, benzodiazepines, antihistamines, serotonin 5-$HT_3$ receptor antagonists, corticosteroids, and other drugs with anti-emetic properties.*
*Analgesics included narcotic and non-narcotic medications.*

Four subjects (1 in the placebo group, 2 in the 10 U/kg BERINERT randomization group, and 1 in the 20 U/kg randomization group had missing data for TtRel, time to initial relief of symptoms, so their primary endpoint value was set to a poor/failure outcome of 24 hours (or 4 hours in the analyses requested by FDA by fax on 21 August 2008).

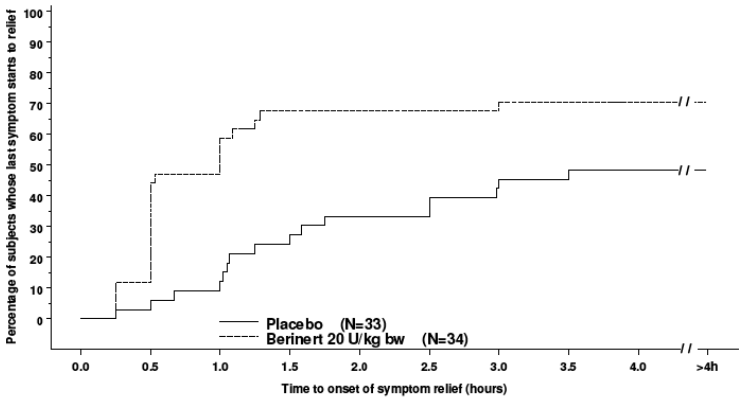
Because of the subjective nature of the primary endpoint (self reported time to start of relief of HAE symptoms), FDA insisted that the protocol for the phase 3 RCT include an assessment of individual HAE symptoms at each time point, in order to correlate these with the primary endpoint. Substantial differences were evident in the results of an analysis of the time to the start of improvement in 1 or more HAE symptoms of the primary attack location (GI or facial, with GI taking precedence in subjects with HAE attack symptoms at both locations) compared to the primary endpoint analysis. Surprisingly, a post hoc analysis proposed by the sponsor, time to start of relief of the <u>*last*</u> HAE attack symptom to improve, showed closer agreement with the primary endpoint, compared to time to start of improvement of the first HAE symptom to improve, which was present at baseline. This underscores that different subjects likely interpreted the primary endpoint question differently. Some subjects may have believed they were only to report start of relief of symptoms if they had experienced at least some relief of ALL

of their HAE attack symptoms. The lack of better correlation between the primary endpoint and the analyses of individual HAE symptoms highlights our incomplete understanding of how best to assess efficacy in this disease.

However, the time to initial reduction by 1 severity category in GI symptoms demonstrated a difference between high dose BERINERT and placebo groups with a p value of 0.02 according to an analysis performed by the CBER Biostatistician during the first review cycle. This analysis did not impute poor/failure values of 24 hours for subjects who used confounding medications between 5 hours prior to ToS and ToSRel. The corresponding difference between these treatment groups for time to initial reduction in facial symptoms was not significant (P ~ 0.6) an analogous analysis.

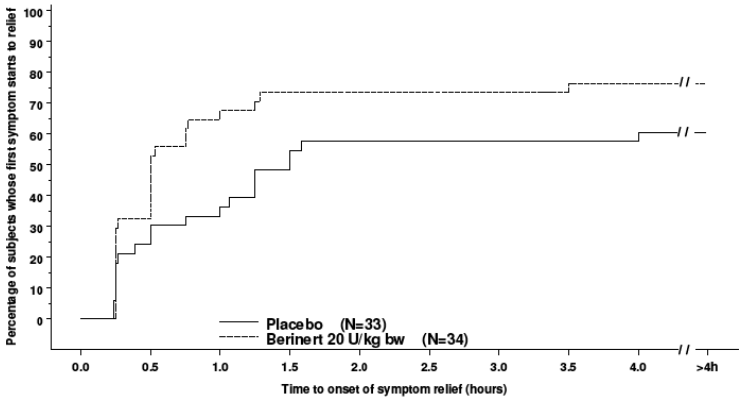
The sponsor's initial review cycle analysis of the primary endpoint for facial attacks showed a non-significant trend favoring BERINERT 20 U/kg (p = 0.16). Masked independent review of serial hourly photographs by the DSMB revealed differences from self-reported time to initial improvement in facial attack symptomatology in several instances that were not always attributable to the less frequent schedule of serial facial photographs (performed at baseline then hourly). Although the numbers of subjects are small, the Kaplan Meier curve of the masked independent review by the DSMB of facial photographs suggested a positive treatment effect in the subgroup of facial attack subjects randomized to BERINERT 20 U/kg vs. placebo.

**Time to Start of Relief of Last Symptom (Abdominal Attacks) with Imputation to > 4 Hours for Subjects Who Received any Rescue Medication*before Start of Relief**




*****_Rescue study medication with C1-INH, analgesics, anti-emetics, open-label C1-INH or fresh frozen plasma. Anti-emetics included antidopaminergics, benzodiazepines, antihistamines, serotonin 5-$HT_3$ receptor antagonists, corticosteroids, and other medications with anti-emetic properties._

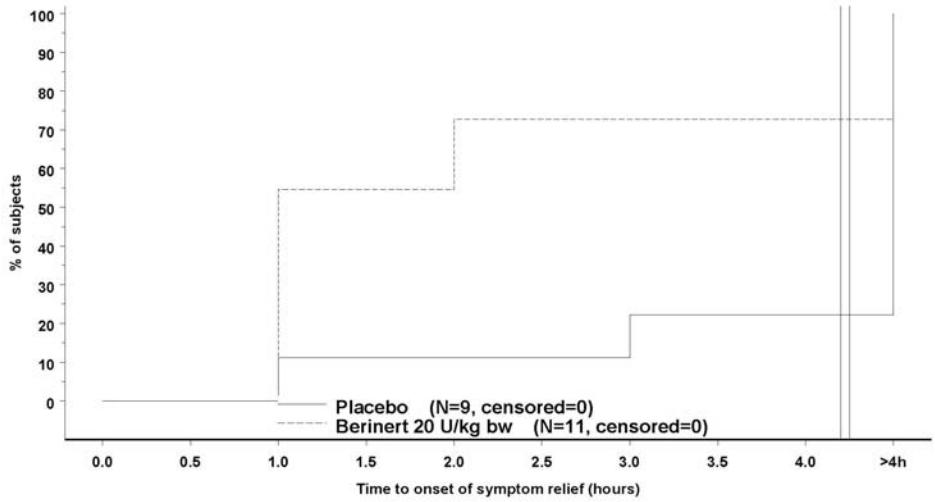
**Time to Start of Relief of First Symptom (Abdominal Attacks) with Imputation to > 4 Hours for Subjects Who Received any Rescue Medication* Before Start of Relief**




**Rescue study medication with C1-INH, analgesics, anti-emetics, open-label C1-INH or fresh frozen plasma. Anti-emetics included antidopaminergics, benzodiazepines, corticosteroids, antihistamines, serotonin 5-$HT_3$ receptor antagonists, and other medications with anti-emetic properties.*

For facial attacks, single HAE symptoms were recorded. In addition, photos were taken at pre-determined time points and assessed by the members of an independent Data Safety Monitoring Board (DSMB), who were blinded as to treatment, center and other outcome measures. The change in the severity of the edema when compared to baseline was assessed on a scale with outcomes "no change", "better", "worse" and "resolved". The following Figure shows the time to start of relief from serial facial photographs by DSMB assessment.

**Time to Start of Relief from Serial Facial Photographs***




**Includes abdominal attacks with concomitant facial attacks.*

The study also had a number of *a priori* exploratory endpoints. The outcome of these exploratory endpoints also generally favored a conclusion of the efficacy of 20 U/kg dosage group over placebo in both the sponsor's revised analyses and the FDA final analyses.

**Changes in HAE Symptoms and Use of Rescue Medication in Subjects Receiving Berinert 20 units/kg Body Weight vs. Placebo**

| Additional Endpoints | 20 U/kg Body Weight BERINERT Group (n=43) | Placebo Group (n=42) |
|---|---|---|
| Onset of symptom relief within 60 minutes after administration of study medication *(post-hoc)* | 25 (58.1%) | 11 (26.2%) |
| Onset of symptom relief within 4 hours after administration of study medication | 28 (65.1%) | 18 (42.9%) |
| Number of vomiting episodes within 4 hours after start of study treatment* | 6 episodes | 35 episodes |
| Worsened intensity of clinical HAE symptoms between 2 and 4 hours after administration of study medication compared to baseline† | 0 (0%) | 12 (28.6%) |
| Number (percent) of combined abdominal and facial attack subjects receiving rescue medication, analgesics, or anti-emetics at any time prior to complete relief of symptoms | 13 (30.2%) | 23 (56.1%) |
| At least one new HAE symptom not present at baseline and starting within 4 hours after administration of study medication | 2 (4.6%) | 6 (14.3%) |

* p-value=0.033

†p-value=0.00008

In addition to a 1-sided p value < 0.0249 for the primary endpoint, the protocol required that, for the study to be considered successful, at least one of two secondary endpoints (either the proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment with BERINERT compared to baseline, or the number of vomiting episodes within 4 hours after start of study treatment)

demonstrate a trend in favor of the high dose BERINERT group over placebo, with a one-sided p value of < 0.1.

As noted in the above table, both of the RCT's secondary endpoints: (a) the proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment compared to baseline, and (b) the number of vomiting episodes within 4 hours after start of study treatment demonstrated trends in favor of BERINERT in comparison to placebo (p values < 0.1). The tables below present additional information regarding responses to treatment.

**Proportion of Subjects Experiencing Start of Self-Reported Relief of Symptoms by 4 hours by Attack Type**

| **Attack Type** | **BERINERT 20 units/kg Body Weight (Abdominal Subjects =34) (Facial Subjects = 9) (Other subjects = 0)** | **Placebo (Abdominal Subjects = 33) (Facial Subjects = 8) (Other subjects = 1)*** |
|---|---|---|
| Abdominal | 70.6 (24%) | 45.5 (15%) |
| Facial | 6 (66.7%) | 3 (37.5%) |

*Laryngeal edema initially classified as facial edema.

**Proportion of Subjects Experiencing Reduction in Severity of at Least One Individual HAE Attack Symptom by 4 hours**

| **Attack Type** | **BERINERT 20 units/kg Body Weight (Abdominal Subjects = 34) (Facial Subjects = 9)** | **Placebo (Abdominal Subjects = 33) (Facial Subjects = 8)** |
|---|---|---|
| Abdominal | 33 (97.1%) | 90.9 (30%) |
| Facial | 66.7 (6%) | 4 (50%) |

The protocol and SAPs contained algorithms for imputing poor/failure values of 24 hours for the primary endpoint, "time to start of relief of HAE symptoms (ToSRel)," for when any of these potentially confounding medications were taken prior to ToSRel. When imputation based on concomitant medication use was taken into account, ToSRel is designated ToSRelP (or TosRel+), which forms the basis of the Kaplan-Meier curves of the primary endpoint in the package insert.

The FDA final statistical analyses were based on revised datasets that the sponsor submitted during the 2nd review cycle in response to information requests following the sponsor's response to a complete review letter issued by FDA at the end of the initial review cycle. The sponsor revised their datasets to reflect information gleaned from a sponsor review of source documents relating to the use of confounding concomitant medications for a large group of subjects from the RCT for whom the investigator had marked on the case report forms (CRFs) that the confounding medication was "ongoing." During the 2nd review cycle, the sponsor submitted new analyses of the primary endpoint of the pivotal trial using the new datasets. These include both the analysis method (designed by the sponsor as "original analysis") described in statistical analysis plan (SAP) version 2.0, which the sponsor confirms was never submitted to the IND or otherwise shared with FDA prior to implantation, as well as what the sponsor terms the FDA-requested "robustness analysis." The latter is regarded as the key primary analysis by the FDA because it more closely follows the protocol.

This SAP version 2.0 was dated 1 week prior to unblinding of the study, but was never submitted to the IND. SAP version 2.0 did not impute 24 hour "poor/failure" values for the primary endpoint for subjects who took non-narcotic analgesics, or for subjects who had their dose of androgens raised prior to enrollment in the RCT. FDA did not accept all analysis features of the SAP version 2.0. The FDA-requested robustness analysis imputes a 24 hour "poor/failure" value for subjects who received non-narcotic as well as narcotic analgesics or anti-emetics between 5 hours prior to ToS and ToSRel, which is in keeping with the spirit of the protocol, as well as for subjects who received any medications "non-permitted" by the protocol within the same FDA-defined time window of interest. The 5 hour prior to the time of administration of blinded study medication starting time period for analysis of confounding medications was conservatively chosen to take into account medications which could have been taken some time prior the time of administration of blinded study medication, but which would exert their pharmacodynamic effect after the time of administration of the randomized test medication.

FDA performed a masked review of the submitted concomitant medication source documents and made further changes to the database of the RCT. These changes were limited to decisions, based on the masked source document review, regarding which subjects should received "poor/failure" imputations for the primary endpoint, based on suspected or confirmed use of confounding "non-permitted" medications or narcotic or non-narcotic analgesics or anti-emetics between 5 hours prior to time of blinded randomized study medication and self reported time to start of relief of HAE attack symptoms.

FDA discovered in reviewing the source documents that very few subjects were treated with study test product in the hospital but rather were mostly treated in clinics. The original version of the RCT protocol required that the severity of the HAE attack be such that hospitalization was needed. This restriction was later removed by protocol amendment. The fact that most study centers were clinics rather than hospitals evidently impacted negatively the quality of the medication source documents, as very few source

documents were submitted that unambiguously establish whether concomitant medications whose classes and actions were identified in the protocol as potentially confounding the evaluation of efficacy of the test product were or were not administered during the time period from 5 hours prior to when randomized masked study test medication was given (ToS) and self-reported start of relief of HAE attack symptoms (ToSRel). Per protocol and SAPs, an assessment of whether potentially confounding concomitant medications were taken during this time period was needed in order to conduct the primary analysis.

In order to account for differences in interpretation of information contained in concomitant medication source documents, FDA performed 1 key analysis of the primary endpoint of the RCT and 2 additional robustness analyses. The p values of statistical significance obtained in all 3 FDA analyses of the RCT study primary endpoint were smaller than the sponsor's primary endpoint analyses, the latter based on the sponsor's revised database.

**For the key FDA analysis of the pivotal study's primary endpoint, the CBER biostatistician obtained a p value of 0.0016.** The sponsor obtained a p value of 0.014 for the "FDA Robustness analysis," which FDA considers to be the key sponsor analysis of the primary endpoint. Differences in sponsor and FDA p values are at least in part attributable to the sponsor imputing a poor/failure value of 24 hours due to use of "discouraged" medications, where there were statements in the provided source documents indicating that such medications were not, or were probably not taken between 5 hours prior to randomized study drug was administered and time to initial relief of symptoms. When using the sponsor's unedited datasets, the FDA biostatistician was able to reproduce the sponsor's 1-sided p value for the primary analysis of 0.014 (The sponsor refers to this as the FDA robustness analysis, because it imputes a poor/failure value of 24 hours if subjects took either narcotic or non-narcotic analgesics between -5 hours and ToSRel). The sponsor also redid its "original" primary endpoint analysis based on the revised database, not imputing 24 hours for subjects only on the basis of having taken non-narcotic analgesics during this time period of interest.

In cases where the source documents bear a statement apparently written contemporaneously with the dates of the trial indicating that no medications were taken by the subject during the period 5 hours prior to ToS, a 24 hour value for the primary endpoint has not been imputed in the FDA analyses, provided no record was submitted indicating that "non-permitted" medication or narcotic or non-narcotic analgesics or medicines with anti-emetic properties were taken in the clinic or hospital prior to ToS.

If the source documents leave doubt as to whether one or more "non-permitted" medications or narcotics or non-narcotic analgesics or medicines with anti-emetic properties started prior to the trial and marked as "Ongoing" on the CRFs and source documents (SDs) may have been taken between – 5 hours and ToS, the FDA statistician has performed 2 additional robustness analyses of the primary endpoint, which gave values of 0.0004 and 0.0053.

**Proportion of Subjects with Facial Attacks Demonstrating Improvement in Serial Facial Photographs by 4 hours[**]**

| Attack Type | BERINERT 20 units/kg Body Weight (Subjects = 9) | Placebo (Subjects = 8) |
|---|---|---|
| Facial | 7 (77.8%) | 2 (25%) |

[**]Based on masked (blinded) evaluation by data safety monitoring board.

**Proportion of Subjects with Abdominal and Facial Attack Receiving Rescue Study Medication or Other Confounding Medications (Narcotic Analgesics, Non-Narcotic Analgesics, Open-Label C1-Esterase Inhibitor, androgens at increased dose, or Anti-emetics) at any Time Prior to Complete Relief of Symptoms****

| Attack Type | BERINERT 20 U/kg Body Weight (Gastrointestinal Subjects =31) (Facial Subjects = 4) | | Placebo (Gastrointestinal Subjects = 23) (Facial Subjects = 4) | |
|---|---|---|---|---|
| | Rescue Medication | Other Potentially Confounding Concomitant Medication | Rescue Medication | Other Potentially Confounding Concomitant Medication |
| Gastrointestinal | 12.9 (4%) | 19.4 (6%) | 52.2 (12%) | 30.4 (7%) |
| Facial | 50 (2%) | 25 (1%) | 75 (3%) | 25 (1%) |

****Only subjects who reported complete relief of symptoms during the clinic phase of the study are included in this analysis.**

FDA noted that the protocol's original interim analysis plan was not followed, in that the sponsor did not revise the sample size of the study upward from 25 subjects per arm to 100 subjects per arm, but rather stopped enrollment after ~ 43 subjects were enrolled into each of the high dose and placebo arms. However, one may regard the fact that the study achieved a high degree of statistically significant difference between high dose and placebo groups (the primary analysis) for the primary endpoint despite a final sample size less than half that recommended on the basis of the first interim analysis, actually provides reasonable confidence that the product is effective.

FDA concurred with the DSMB's recommendation to stop enrollment in the low dose arm after the interim analysis during the IND phase, but because of a lag in IRB approvals of the amendment ending enrollment in the low dose arm, nearly as many low dose subjects were enrolled as high dose subjects. Thus, the sponsor's finding that the study failed to find a statistically significant difference in the primary endpoint between low dose (10 Unit/kg) and placebo groups, is of particular interest, especially because 10 U/kg has been the standard dose of the product used in Europe. The pivotal study did not support the efficacy of the 10 U/kg dose studied in the low dose group of the pivotal trial. As noted above, the international package insert was revised by the sponsor after

completion of the RCT to increase the recommended initial dose of the product to 20 U/kg from 10 U/kg.

Because of its uncontrolled and open-label design, efficacy data from the single arm open label extension study was not considered contributory to the evaluation of efficacy, although there was no evidence from the study that the efficacy of the product decreased with successive treatment courses for successive attacks.

FDA concluded from the totality of the data that BERINERT when given within 5 hours of onset of acute facial or abdominal HAE attacks is effective in hastening the start of relief of HAE attack symptoms. It was evident among placebo subjects that the natural history of the course of resolution of abdominal and facial attacks differs. Because of the greater uncertainty in the "point estimate" for time to initial relief of symptoms of facial attacks compared to abdominal attacks, the sponsor has agreed to conduct a post marketing commitment study to further evaluate the efficacy of the product in the treatment of acute facial HAE attacks.

# 7. Safety

Safety data of varying completeness was provided in the original BLA submission for the following studies, which includes several studies outside the HAE attack treatment indication.

**Table of Clinical Studies**

| Study Number | Object. | Design | Products, Arms | Number Subjects | Type Subjects | Duration Treatment |
|---|---|---|---|---|---|---|
| CE1145_3001 | S&E abd or facial HAE Attacks | R, DB, PC, dose-ranging Parallel | Saline<br>BERINERT 10 U/kg<br>BERINERT 20 U/kg | 125 | HAE | Single administration With optional blinded single rescue dose |
| CE1145_3003 | Any HAE attack | Open Label, un-controlled | BERINERT 20 U/kg | 39 as of June '07 | HAE | Ongoing |
| 7MN-401CI-OB<br>7MN-402CI-OB | HBV safety | Open Label, un-controlled | C1-INH 500-1000U IV | 9<br><br>4 | HAE, hered. or acquired | Single dose<br><br>10-16 months |
| 7A-202CH-B | ----b(4)---- | R, DB, PC | C1-INH 3500 U, 1.1% HSA | 15 per Group | ----------b(4)---- | Single dose |
| 7B-201CH-C | ----b(4)---- | R, DB, PC | C1-INH 2500 U, 1000 U 1.1% HSA | 15 per group | ----------b(4)---- | Single treatment scheme |
| 7D-201CI-OB | Efficacy, Tolerance | Open label, un-controlled | C1-INH 500 – 1000 U per | 7 | HAE | 1-5 injections per subject |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | dose | | | |
| CE-1145_6001 | Efficacy, Safety | Retrospective Case Collection | C1-INH 500-1000 U/dose | 20 | Pregnant with HAE | 3-10 months during pregnancy |

Placebo-controlled Clinical Study (RCT)

In the placebo-controlled clinical study - referred to as the randomized clinical trial (RCT), 124 subjects experiencing an acute moderate to severe abdominal or facial HAE attack were treated with BERINERT (either a 10 unit per kg body weight or a 20 unit per kg body weight dose), or placebo (physiological saline solution).

Clinic visits occurred following discharge, at day 7-9, and at week 12 (the latter for viral safety and SAEs only).

The following safety endpoints were incorporated into the RCT design:

- Viral safety testing by both -b(4)- and serology for the following viruses at baseline, day 9 for parvo B19 (-b(4)- only), and week 12 for HIV 1&2, HAV, HBV, and HCV.
- AEs
- Vitals, including temperature and RR q 1 hour x 4, then q 4 hr until 24 hours or discharge.
- Serum amylase
- CBC baseline only!
- Urinalysis baseline only
- Serum troponin baseline only
- ECG at baseline only
- Serum anti-C1-Esterase Inhibitor antibodies were not requested in the protocol, but were done on Canadian site subjects (n = 5), and periodic anti-C1 Esterase Antibodies were added to the open-label extension study.
- Diary cards were used to record complete resolution of attack, concomitant meds through day 7-9, and any Aes through day 7-9.

Eight/127 (6.3%) subjects did not complete the treatment and/or f/u phases. Of these, 4 withdrew consent and 4 were lost to follow-up. All 8 of these subjects were included in the ITT population. The per-protocol population contained 121 subjects (6 were excluded). The size of the overall (combined treatment group) safety populations (4 hour and after 4 hour) was larger by 3 subjects than the total of the placebo, BERINERT 10 U/kg, and BERINERT 20U/kg randomized safety populations because 1 subject in the placebo group, 1 in the BERINERT 10 U/kg group, and 1 non-randomized subject received > 15U/kg BERINERT.

The treatment-emergent serious adverse reactions/events that occurred in 5 subjects in the RCT were laryngeal edema, facial attack with laryngeal edema, swelling (shoulder and chest), exacerbation of hereditary angioedema, and laryngospasm. One case of laryngospasm that occurred ~ 6 weeks after administration of BERINERT 20 U/kg and, considered a serious adverse event (SAE), was reported in a subject and was considered not related.

During the first 4 hours after test product administration, 10/46 (22%) subjects in the BERINERT 20U/kg group (4 hour safety population) experienced AEs, compared with 18/41 (44%) of placebo subjects. The number of subjects with AEs considered by the investigator as at least possibly related to the test article was 5/46 (11%) in the BERINERT 20 U/kg group compared with 8/41 (20%) in the placebo group (4 hour safety population).

**Adverse Reactions[#] Occurring up to 4 hours after Initial Infusion in More than 4% of Subjects, Irrespective of Causality[*]**

| Adverse Event | Number (%) of Subjects Reporting AE BERINERT 20 units/kg (n = 43) | Number (%) of Subjects Reporting AE [Placebo] (n = 42) |
|---|---|---|
| Nausea[*] | 3 (7%) | 5 (11.9%) |
| Dysgeusia | 2 (4.7%) | 0 (0) |
| Abdominal Pain[*] | 2 (4.7%) | 3 (7.1%) |
| Vomiting[*] | 1 (2.3%) | 3 (7.1%) |
| Diarrhea[*] | 0 (0) | 4 (9.5%) |
| Headache | 0 (0) | 2 (4.8%) |

[#]The study protocol specified that adverse events which began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (i.e. adverse reactions).

[*]The following abdominal symptoms were identified in the protocol as associated with HAE abdominal attacks: abdominal pain, bloating, cramps, nausea, vomiting, and diarrhea.

**Adverse Reactions[#]* Occurring in More than 4% of Subjects up to 72 hours after Infusion of Initial or Rescue Medication[*] by Intent-to-Treat, Irrespective of Causality**

| Adverse Event | Number (%) of Subjects Reporting AE[*†] BERINERT 20 units/kg (n = 43) | Number (%) of Subjects Reporting AE*[†] [Placebo] (n = 42) |
|---|---|---|
| Nausea | 3 (7%) | 11 (26.2%) |
| Headache | 3 (7%) | 5 (11.9%) |
| Abdominal Pain | 3 (7%) | 5 (11.9%) |
| Dysgeusia | 2 (4.7%) | 1 (2.4%) |
| Vomiting | 1 (2.3%) | 7 (16.7%) |
| Pain | 1 (2.3%) | 4 (9.5%) |
| Muscle spasms | 1 (2.3%) | 4 (9.5%) |
| Diarrhea | 0 (0) | 8 (19%) |
| Back pain | 0 (0) | 2 (4.8%) |
| Facial pain | 0 (0) | 2 (4.8%) |

[#]The study protocol specified that adverse events which began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (i.e. adverse reactions).

[*]If a subject experienced no relief or insufficient relief of symptoms within 4 hours after infusion, investigators had the option to administer a blinded second infusion ("rescue" treatment) of BERINERT (20 units/kg for the placebo group, 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group).

[†]AEs following either initial treatment and/or blinded "rescue" treatment. Because more subjects in the placebo randomization group than in the BERINERT randomization group received rescue treatment, the median observation period in this analysis for subjects randomized to placebo was slightly longer than for subjects randomized to receive BERINERT.

In the after 4 hour safety population, among subjects without rescue medication, there were 2/38 possibly related AEs in the BERINERT 20U/kg group and none in the placebo or BERINERT 10 U/kg groups. In the same safety population, among subjects who received rescue medication, there was 1 subject in each randomization group who reported an AE considered by the investigator to be at least possibly related to test article.

The next Table lists the Adverse Events (AEs) that occurred in more than 4% of the subjects 7 to 9 days after the end of a BERINERT infusion, *irrespective of causality.*

**Adverse Events Occurring in More than 4% of Subjects* Receiving BERINERT at either 10 units/kg or 20 units/kg 7 to 9 Days after Infusion*, Irrespective of Causality***

| Adverse Event | Number of Subjects Reporting AE (n=108) | Percent |
|---|---|---|
| Hereditary angioedema | 12 | 11.1 |

| | | |
|---|---|---|
| Headache | 12 | 11.1 |
| Abdominal pain† | 7 | 6.5 |
| Nausea† | 7 | 6.5 |
| Muscle spasms | 6 | 5.6 |
| Pain | 6 | 5.6 |
| Diarrhea† | 5 | 4.6 |
| Vomiting† | 5 | 4.6 |

*****Includes subjects in the placebo group who received BERINERT 20 units/kg as rescue study medication.

†These symptoms were identified in the protocol as related to the underlying disease. Any increase in intensity or new occurrence of these symptoms after study medication administration was considered to be an AE.

# 8. Advisory Committee Meeting

Referral to the Blood Products Advisory Committee (BPAC) prior to licensure was not recommended based on the following justification:

• New molecular entity (NME) provision does not apply to BERINERT as another plasma-derived C1 esterase inhibitor product was recently presented at BPAC on May 2, 2008 for prophylaxis of acute attacks of hereditary angioedema.

• The mechanism of action and function of C1-esterase inhibitor in the blood complement, coagulation, and fibrinolytic cascades are well studied and understood.

• Plasma-derived C1-esterase inhibitor concentrates have been used to treat HAE attacks for over 25 years in countries where these products are available.

• BERINERT is a plasma-derived C1-esterase product from US Source Plasma and has been approved for many years in Europe.

• The study design to evaluate efficacy of BERINERT was adequate and the results of the study did not raise any concerns related to safety. BERINERT has demonstrated a favorable safety profile.

• Review of information submitted in the BLA for BERINERT indicated efficacy for the overall study population of subjects with abdominal and facial attacks, as well as the subgroup of subjects with abdominal attacks. BPAC discussion of this application is unlikely to change the outcome of the review of this file from a regulatory standpoint.

• BERINERT is the first C1 esterase inhibitor product approved for acute treatment of HAE attacks and, therefore, it is in the interest of the public health not to delay licensure by requiring consideration by BPAC of this application.

# 9. Pediatrics

BERINERT was granted orphan drug status on October 16, 1992. Pediatric Research Equity Act (PREA) does not apply to orphan indications.

# 10. Other Relevant Regulatory Issues

No other relevant regulatory issue to disclose

# 11. Labeling

The sponsor's proprietary name, BERINERT, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective during the first and second review cycles and was found to be acceptable upon initial review on September 30, 2008 and remained acceptable upon re-evaluation on August 20, 2009. OBBR concurred.

Full Prescribing Information (FPI): APLB reviewed the original FPI submitted by the applicant. Comments from a promotional and comprehension perspective were provided to OBRR on May 22, 2008. Comments regarding the FPI were conveyed to the applicant on November 5 and November 6, 2008. The applicant subsequently submitted a revised FPI. APLB reviewed the revised FPI on August 20, 2009 and provided additional comments to OBBR for discussion with the applicant. FDA's comments were conveyed to the applicant on August 11, August 14, September 17, September 18, September 28, October 2, and October 6, 2009. The applicant accepted all of FDA's remaining comments and recommendations. All FPI issues have been adequately resolved to proceed with final approved labeling.

Carton and immediate container labels submitted in the original application were reviewed by APLB. Comments on them from a promotional and comprehension perspective were provided on October 15, 2008 (for original submission) and August 20, 2009 (for revised submission). The applicant submitted revised carton and container labeling that APLB reviewed on July 23, 2009. The applicant accepted all outstanding recommendations. All carton/container labeling issues were adequately resolved.

Patient labeling/Medication guide: Patient Information was included in all reviews of the FPI under Section 17 of the FPI. All issues were adequately resolved.

# 12. Post-Marketing Studies

**Rationale for requiring post-marketing studies:**

Immunogenicity data were limited with respect to the numbers and percentage of hereditary angioedema subjects enrolled in clinical trials who underwent assessment of serum anti-C1-Esterase Inhibitor antibodies before and after multiple exposures to BERINERT. Despite these limitations, a ~ 20% incidence of treatment-emergent anti-C1 Esterase Inhibitor antibodies has been observed thus far in the sponsor's open-label extension study (IMPACT II). Additional human immunogenicity data were requested and agreed to by the sponsor by post-marketing commitment in order to better determine whether antibody development is associated with adverse events, i.e. acute hypersensitivity reactions and/or inadequate therapeutic response.

A few cases of suspected viral transmissions by the product have been reported during foreign post-marketing pharmacovigilance. The information presented in these cases was not sufficient to conclusively determine whether BERINERT was responsible for the transmissions. An active surveillance plan will facilitate discovery of potential viral transmissions by the product.

Use of BERINERT at higher than recommended doses has been associated with fatal thrombotic events in a clinical trial of pediatric subjects where the product was administered for an indication other than HAE. The minimum dose of this product associated with thrombotic events is unknown. FDA determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA would not be sufficient to identify an unexpected serious risk when available data indicates the potential for a serious risk, i.e. thrombosis , with the use of the product when administered at higher than labeled dose schedules. This is in part due to the limited target population of patients with hereditary angioedema as well as known under-reporting of adverse reactions in the voluntary post-marketing pharmacovigilance setting.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, the sponsor was required to conduct the following studies:

**Post Marketing Requirements**

**1. Inhibitory Antibody Study**

CSL Behring is required to submit a protocol to assess inhibitory antibody formation against C1-Esterase Inhibitor. The time points for assessing the formation of antibodies shall be determined during protocol design negotiations. Subjects with antibodies positive by -b(4)- would be tested for inhibitory antibodies using a validated assay. The study report will present aggregate immunogenicity data on a minimum of 40 subjects (for whom immunogenicity data has not already been submitted in the BLA) who have anti-C1 Esterase Inhibitor antibody testing prior to and following repeated exposures to

BERINERT. The study report will also describe attempts to correlate treatment-emergent antibodies with adverse events (AEs). These studies will be conducted according to the following schedule:

Protocol Submission: Within 180 days of licensure.
Study Start Date: Within 90 days of acceptance by FDA of the final protocol.
Final Report Submission: Within 80 months of initiation of the study.

**2. Completion of Planned Ongoing Open Label Extension Study CE1145_3003 (IMPACT II)**

The ongoing open label extension study, CE1145_3003 (IMPACT II) will provide long term safety data in subjects who have received repeated administrations of BERINERT. This will enhance our ability to detect adverse events that may be related to anti-C1-Esterase Inhibitor antibody development, and will also provide additional power to detect lower frequency adverse events, such as thrombotic events that might occur even at currently recommended doses when a monitored study population is observed following multiple repeated administrations of the study product.

Protocol Submission: August 12, 2005.
Study Start Date: Protocol initiated, study ongoing.
Final Report Submission: Within 12 months of study completion.

**3. HAE Patient Registry**

CSL Behring is required to conduct a study consisting of establishing and maintaining a registry of patients treated with BERINERT for any indication. Variables to record as part of the registry include: indication for BERINERT, administered doses, patient demographics, concomitant medications and plasma products, adverse events, including possible thrombotic or embolic events, and results of any viral testing. The use of a structured questionnaire should be considered in conjunction with the registry. The registry should permit a mechanism for enhanced detection of thrombotic and thrombo-embolic events. A patient registry will also facilitate discovery and reporting of potential viral transmissions by the product. HAE is a very rare disease, and increased reporting of associated safety problems may be achieved by use of a patient registry. CSL Behring would maintain this registry for 36 months after market application approval.

Registry development: Within 6 months of product licensure.
Registry Implementation: Within 6 months of product licensure.
Duration: 36 months from product licensure.
Submission of Final Study Report on Registry within 48 months from product licensure, to include analysis of registry data and all raw data in electronic format.

**Agreed Upon Post Marketing Commitments**

In addition to the clinical PMRs, the sponsor agreed to the following postmarketing commitments regarding BERINERT:

4. CSL Behring commits to submit a protocol within 180 days of receipt of this letter for conducting a clinical development program to further evaluate the efficacy of the product in acute facial HAE attacks and to obtain additional immunogenicity data.

Acute Facial HAE Attack Study
The acute facial HAE attack study would be a randomized masked study that would be adequately powered to evaluate the efficacy of BERINERT for facial HAE attacks. The primary endpoint is to be finalized during protocol design negotiations.

In the final study report, the use of potentially confounding medications will be compared across randomization groups.

Protocol Submission: Within 180 days of licensure
Study Start Date: Within 90 days of acceptance by FDA of the final protocol.
Final Report Submission: Within 80 months of initiation of the study.

5. ----------b(4)----------

6. Post-Licensure Pharmacovigilance Plan

CSL Behring submitted a Post-Licensure Pharmacovigilance Plan as amendment 37 to the BLA on 02 September 2009 (received by FDA on 04 September 2009).

FDA requested the sponsor develop and implement a Post-Licensure Pharmacovigilance Plan based on the review committee's assessment that a pharmacovigilance plan will be needed to assess:

(a) a serious risk of thrombosis, as seen with this product when the product was administered at higher than labeled doses.

(b) suspected viral transmissions by the product. As noted above, a few cases of suspected viral transmissions by the product have been reported during foreign post-marketing pharmacovigilance. The information presented in these cases was not sufficient to conclusively determine whether your product was responsible for the transmissions.

(c) whether the product is associated with additional serious or medically significant adverse reactions that might result from the development of anti-C1 Esterase Inhibitor Antibodies or from any of the multiple known mechanisms of action of the product. The

pharmacovigilance plan is designed to facilitate discovery, analysis, and reporting of adverse reactions.

CSL Behring has agreed to implement a post-licensure pharmacovigilance plan per the ICH E2E Pharmacovigilance Planning guidance within 6 months of application approval, to monitor long-term safety with the use of BERINERT. The major components of this pharmacovigilance plan include routine pharmacovigilance (i.e., compliance with applicable post-market reporting requirements under FDA regulations), with the exception that all thrombotic or thrombo-embolic adverse events or possible viral transmissions by the product must be reported to FDA as either 7 or 15 day safety reports.

Plan Submitted on 02 September 2009 (received by FDA on 04 September 2009).
Plan implementation: Within 6 months of product licensure.
Duration: Implementation of the plan is open-ended.

# 13. Recommendation

Approval