

**Medical Officer Clinical Final Review of ORIGINAL BLA
OBRR/DH**

BLA 125287 LOGIN ID --b(4)--

See also: IND -b(4)-, including Amendments 45 (final protocol) and 50 (preliminary report of phase II/III trial and its extension study)

Sponsor: CSL Behring LLC

Sponsors Point of Contact: Hartmann RPh, Paul R

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CBER Receipt Date: 07 March 2008

Letter Date: 06 March 2008

Fast Track Application: No.

Fast Track Request Denied and Denial Communicated to Sponsor

Priority Review Status: Requested by sponsor with supporting information in Attachment 1, Module 1.

Orphan Drug Status: Granted 16 October 1992 for “Prevention and/or treatment of acute attacks of hereditary angioedema.”

PREA Status: Full waiver requested in cover letter to BLA, due to orphan drug designation.

Gene Therapy, Somatic Cell Therapy or Xenotransplantation: N/A

Proper Name: C1-Esterase Inhibitor (Human), Pasteurized

Proposed Trade Name: (Berinert)

Product Formulation: Lyophilized powder for reconstitution and intravenous administration

The product is manufactured in Marburg, Germany and is provided in lyophilized vials containing 500 U to be reconstituted with 10 mL of

SWI, yielding 50 U/mL. It is a “pasteurized” product lacks the 2 “orthogonal” viral inactivation steps typical of more modern plasma-derived products.

Proposed Use (Indication): For the treatment of acute attack episodes in patients with hereditary angioedema (HAE)

Proposed Treatment Population: Patients experiencing acute attacks of HAE (abdominal and facial attacks studied)

Product Type: BLOOD /Sub type: OTHER/C1-INHIBITOR

Pharmacologic Class or Category: C1-INHIBITOR

Review Team:

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Pivotal Phase II/III Clinical Protocol:

Protocol ID: **CE1145_3001**

Protocol Name: Human pasteurized C1 esterase inhibitor concentrate (CE1145) in subjects with congenital C1-INH deficiency and acute abdominal or facial HAE attacks.

Pivotal Trial: Yes, but my IND review memos state that additional discussion was needed to determine whether a single pivotal trial in combination with foreign post-marketing data would suffice to provide substantial evidence of efficacy and safety.

Date Review Completed: See Medical Reviewer Signature Stamp

| <u>Table of Contents</u> | <u>Page</u> |
|--|--------------------|
| Executive Summary | 8 |
| Comments and questions for the applicant | 10 |
| Significant Findings from Other Review Disciplines | 11 |
| Chemistry, Manufacturing and Controls (CMC) | 12 |
| Animal Pharmacology/Toxicology | 12 |
| Clinical and Regulatory Background | 25 |
| Disease or Health-Related Condition(s) Studied and Available Interventions | 29 |
| Important Information from Pharmacologically Related Products, Including Marketed Products | 29 |
| Previous Human Experience with the Product Including Foreign Experience | 30 |
| Regulatory Background Information (FDA-Sponsor Meetings) | |
| Clinical Data Sources (both IND and non-IND), Review Strategy and Data Integrity | |
| Material Reviewed | |
| BLA/NDA Volume Numbers Which Serve as a Basis for the Clinical Review | |
| Literature, if Applicable | 35 |

| | |
|---|----|
| Post-Marketing Experience, Foreign | 35 |
| Table(s) of Clinical Studies | 35 |
| Review Strategy | 36 |
| Good Clinical Practices (GCP) and Data Integrity | 37 |
| Financial Disclosures | 38 |
| Human Pharmacology (Immunogenicity, Pharmacology, Pharmacokinetics, etc., as relevant) (Note: You may refer to section 8.) | 38 |

| | | |
|---|--|------------|
| | Trial # 1 (IMPACT I) | 39 |
| | Applicant's Protocol # and Protocol Title | |
| | Objective/Rationale | 40 |
| | Design Overview | 40 |
| | Population | 42 |
| | Products mandated by the protocol | 43 |
| | Endpoints (how measured, appropriateness) | 45 |
| | Surveillance | 45 |
| | Statistical considerations | 47 |
| | Results, by Trial | |
| | Populations enrolled/analyzed | 50, 56 |
| | Efficacy endpoints/outcomes | 54 |
| | Safety outcomes | 62, 66 |
| | Safety Update | 72, 83, 87 |
| | Comments & Conclusions | 66 |
| | Trial # 2 (IMPACT II – Open-Label Extension of Phase II/III Study) | 76 |
| 9 | Overview of Efficacy Across Trials | 81 |
| | Indication # I | |
| | Methods | 81 |
| | Efficacy Findings | 97 |
| | Safety in Small Foreign Studies in Various Indications | 94 |
| | Overview of Safety Across Trials | |
| | Safety Database - Number of Subjects, Types of Subjects and Extent of Exposure | 72 |
| | Safety Assessment Methods | 72 |
| | Significant/Potentially Significant Events | |
| | Deaths | 72 |
| | Other Significant/Potentially Significant Events | 72 |

| | |
|---|---------|
| Dropouts | 83 |
| Other Safety Findings | |
| ADR Incidence Tables (Local & Systemic Events) | 104 |
| Laboratory Findings, Vital Signs | 84 |
| Product-Demographic Interactions (e.g., Age, Gender, etc.) | 141 |
| Product-Product Interactions | 87 |
| Immunogenicity (Therapeutic Proteins) | 84 |
| Human Reproduction and Pregnancy Data | 94 |
| Overdosage Exposure | 94 |
| Post-marketing Exposure | 30 |
| Safety Conclusions | 99 |
| Additional Clinical Issues | |
| Special Populations | 141 |
| Pediatrics | 87, 141 |
| Conclusions – Overall | 8, 96 |
| Recommendations | 12 |
| Recommendation on Postmarketing Actions | 27 |
| Labeling – See separate labeling review/revised draft package insert. | |

Executive Summary:

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 interim results from the 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 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). 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. The CBER review team has thus far been unable to completely validate the sponsor's primary endpoint analyses, the reason for which is explained toward the end of this summary.

Time to onset of relief of abdominal or facial HAE symptoms by subject assessment¹ (ITT, from sponsor's table 13 on p 74 of study report)

| | Placebo N = 42 | Berinert 10 U/kg N = 39 | Berinert 20 U/kg N = 43 |
|----------------|-------------------|----------------------------|----------------------------|
| Mean (SD) | 10.3 (11.5) | 7.5 (10.5) | 3.9 (8.2) |
| Median (range) | 1.5 (0.20 – 24.0) | 1.2 (0.17 – 24.0) | 0.5 (0.17 – 24.9) |

¹As admitted by the sponsor in amendment 16, the results for group mean times to onset of relief are biased by the assignment of an imputed value of 24 hours for time to initial relief of symptoms for subjects who received rescue medication after 4 hours or who received either open label Berinert or analgesics/anti-emetics before 4 hours are biased. One cannot know what the time to onset of relief of symptoms would have been for such subjects had they not received rescue medication or the confounding concomitant medications.

Dose finding – primary endpoint, ITT population

| Comparison of time to initial relief of HAE symptoms | P value |
|--|------------|
| Berinert 10 U/kg vs. Placebo | P = 0.273 |
| Berinert 20 U/kg vs. Placebo | P = 0.0025 |
| Berinert 20 U/kg vs. Berinert 10 U/kg | p = 0.0048 |

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).

According to the sponsor, 4 subjects received open-label Berinert or other medications prior to self-reported time to relief of symptoms, which resulted in imputation of a “poor-failure” outcome of 14 hours

for the primary endpoint, time to initial relief of symptoms (TTRELP, also called TTREL+).

Review of the time to reduction by 1 severity category in GI symptoms revealed differences between this FDA-generated post-hoc robustness outcome measure and the self-reported primary endpoint of time to initial relief of symptoms in 49% of subjects. 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 Dr. Wang of this Center. The corresponding difference between these treatment groups for time to initial reduction in facial symptoms was not significant ($P \sim 0.6$) in Dr. Wang's analysis. The sponsor's 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).

The proportion of subjects who received rescue medication, analgesics, anti-emetics, or open label CTM at any time was statistically significantly greater in the placebo group than in the Berinert 20 U/kg group in the sponsor's analysis. The CBER review team was unable to locate databases with the needed fields and values in those fields to be able attempt to validate this sponsor's analysis.

The number and proportion of subjects in the placebo group who received blinded rescue study medication was ~ 2.5 times greater than the corresponding number and proportion of subjects in the Berinert 20 U/kg group, supporting the efficacy of Berinert 20 U/kg.

Post-hoc landmark analysis – Number and Percentage of subjects by treatment group who reported time to onset of relief of HAE attack symptoms by 4 hours (ITT)¹.

| Randomization Group | Proportion (percent) of subjects reporting initial relief of HAE symptoms by 4 hours |
|---------------------|--|
| Placebo | 25/42 (59.5%) |
| Berinert 10 U/kg | 28/39 (71.8%) |
| Berinert 20 U/kg | 37/43 (86.0%) |

¹Subjects receiving open-label Berinert, masked rescue medication early (protocol violation), anti-emetics, or analgesics prior to reporting onset of relief of HAE attack symptoms received an imputed time to initial relief of symptoms of > 4 hours. Source: Abstracted from Figure 11.1.1 study report.

The study also had a number of *a priori* exploratory endpoints. The outcome of several of these exploratory endpoints also favored the 20 U/kg dosage group over placebo. The sponsor notes that identical results for the median time to initial relief of symptoms were achieved in the open-label extension study and in the pivotal phase 3 study.

It was not possible to validate the sponsor's breakdown of the administration of "any rescue medication" prior to initial relief of symptoms, or prior to complete relief of symptoms, because of the large amount of missing data entries for the start time and date of "discouraged" (anti-emetics and analgesics) and "Non-permitted" medications noted to have been administered in the concomitant medication database, ADCM. Although the sponsor representative stated in a teleconference held with Dr. Wang and Ms. Valencia of this Office with the sponsor on 12 November 2008 that they imputed "poor/failure" outcomes of 24 hours for the primary endpoint analysis, time to initial relief of symptoms, for all subjects who received any of the 6 categories of medications "Non-permitted" by the protocol, Appendix IVb: "Impact of Concomitant Medications and Rescue medication on PP- and sub-population definition and on primary efficacy variable" (Original BLA submission Module 5, section 5.3.5.1.11.22) indicates that this was not the case, and that the key variable TTREL+ did not take into account androgens or transexamic [sic] (tranexamic) acid or aminocarproic [sic] (aminocaproic) acid. This appendix was appended to version 2.0 of the statistical analysis plan dated 26 October 2007, approximately 1 month before the last subject completed the day 7-9 follow up visit. A review of BIRAMS does not indicate that this final statistical analysis plan was ever submitted to the IND.

During the same 12 November 2008 teleconference, I inquired why there were a large number of analgesics, anti-emetics and medications "Non-permitted" by the protocol that were missing start date/time values. The sponsor representative explained that in a number of such instances, the original CRF showed such medications were being taken prior to the study and were

“continuing.” In these cases, the sponsor sent a query form to the investigators asking them if they administered the product during the acute phase of the HAE attack. In the majority of such cases, the investigators replied “no.” Because this information may have been collected after the study blind was unbroken, and because the queries may have been made in a selective fashion, and because we were told that in the majority of instances the responses to the investigator queries may have conflicted with the information on the original CRFs, the sponsor is asked to obtain and provide copies of hospital medication records for all analgesics, anti-emetics, open-label C1-Inhibitor, and the 6 classes of medications “Non-permitted” by the protocol for the period from 5 hours prior to the start of administration of blinded study medication and up to 24 hours after the time of administration of study medication at time 0. The sponsor is also asked to compile these data into an analysis-ready dataset and include the date of the start of randomized study medication and the date the investigator filled out the data query form for concomitant medications whose administration may confound the interpretation of efficacy of Berinert.

Significant Findings from Other Review Disciplines

Chemistry, Manufacturing and Controls (CMC)

The kinetics of HIV inactivation by the sponsor’s heat treatment viral inactivation step are unusually slow. The sponsor attributes this to HIV binding to and stabilization by C1-Inhibitor. The sponsor has been asked to submit complete validation data for an additional viral removal/inactivation step, such as ammonium sulfate precipitation to be reviewed prior to consideration of licensure, and also to commit to ----b(4)-----
----- as a post-marketing commitment (PMC).

Animal Pharmacology/Toxicology

See animal pharmacology/toxicology memo.

Reviewer Signature:

Supervisory Concurrence:

1st Level Review

Supervisor Name:

Supervisor Title:

Concur _____ Not Concur _____

Supervisory Signature:**Recommendation:**

A complete review letter is recommended at this time. The BLA may be approved from the medical perspective once the sponsor (a) provides an adequate analysis-ready dataset including all raw data variables needed to validate all derived data variables needed to permit verification of the sponsor's primary endpoint analysis and (b) submits a revised draft package insert as recommended in my separate labeling review memo. The revised draft package insert should include the updated results of the primary endpoint analysis taking into account actual times of administration of potentially confounding analgesics, anti-emetics, and medications "Non-permitted" according to the protocol, as determined by review of hospital medication source records.

Letter-ready comments:

1. It appears that the study protocol was not followed for performing analyses of the primary efficacy endpoint for pivotal study CE1145_3001. Based on the information provided to date in your original BLA and amendments, we have been unable to validate that your primary endpoint analyses have been conducted according to the protocol and/or statistical analysis plan. More specifically:
 - The protocol indicates that subjects who received analgesics or anti-emetics prior to reporting time to start of relief of symptoms were to have a "poor/failure" value of 24 hours imputed for the primary endpoint variable. We note that for variables "CMSTDI" (Start Date of Medication -b(4)-date)"CMSTTI" (Start Time [of concomitant medication]), and "TOANALG" ("Date/Time of first analgesic after start of first administration in the respective time window") in the ADCM concomitant medications database there are large numbers of concomitant medications with analgesic or anti-emetic pharmacologic properties for which the values of one or all these key variables are missing.
 - In Amendment 17 submitted September 12, 2008, p 2 of "Guide to datasets and programs for additional analysis required by FDA fax dated 21Aug2008" it states that:
 - i. "All programs and study specific macros used for the additional efficacy analysis of study CE1145_3001 can be found in "STATISTICAL\FDA_21Aug2009\PROGRAMS" and

that “Data preparation programs were used to create new permanent analysis datasets available in the folder “STATISTICAL\FDA_21Aug2009\DATASETS\ANALYSIS.”

- ii. “To obtain correct results the data preparation programs need to be used in the specified sequential order as indicated in the document “LIST_OF_PROGRAMS.PDF.”

Please be advised that “LIST_OF_PROGRAMS.PDF appears to be missing from the CD-ROM submitted as part of Amendment 17.

- We understand from our telephone conversation held on November 12, 2008 with representatives of your firm and of --b(4)---, your Contract Research Organization which performed statistical analyses for this BLA, that some investigators had indicated on the original CRFs (Case Report Forms) for a number of anti-emetics, analgesics, and/or medications “Non-permitted” by the protocol until after complete resolution of the HAE attack, for several subjects, these medications were being taken at screening and were marked as “continuing” to be administered. You indicated during the teleconference that, in these instances, you sent the investigators in question query forms asking them whether the medications in question had been administered during a particular “unspecified” time frame during the acute attack. You indicated that the majority of these queries were answered by the investigators as “no.”

We request you submit

- a printed table and database showing the original CRF entries for “any rescue medication” (i.e, any medications with analgesic or anti-emetic properties (“discouraged medications”) or “Non-permitted medications” which, according to the original CRF entries, were being taken at subject screening or at the time of randomization including:
 - separate columns showing the updated information received in response to your queries to investigators.
 - additional columns showing the dates of subject screening, randomization, and the dates

the investigators provided their responses to your queries about these medications.

- For any instances where these medications were indicated on the original CRF entries as “continuing” or being continued, we request you submit
 - copies of the actual hospital medication records for the 5 hour period preceding and the 24 hour period following the time of administration of randomized masked (blinded) study medication
 - printed table and database showing the times of administration of “any rescue medication (i.e, any medications with analgesic or anti-emetic properties (“discouraged medications”) or “Non-permitted medications.” “Any rescue medication” should include, but not be limited to, the list of concomitant medications provided to you by us on November 13, 2008 in an Excel spreadsheet entitled “ForbiddenMeds.xls.”
- We note that, whereas the protocol explicitly indicated that administration of “analgesics” prior to the subject’s self-reported time to start of relief of HAE attack symptoms was to result in imputation of a “poor/failure” value for the primary endpoint for such subjects, the variable “TtRel+” (also variously called “TTRELP,” etc.) was not affected if the subject was given non-narcotic analgesics. We request you re-analyze the study primary endpoint, taking into account “any rescue medication,” including non-narcotic analgesics, anti-emetics, and all “Non-permitted” medications. The use of “any rescue medication” may otherwise confound the interpretation of the primary endpoint.
- In partial response (September 3, 2008) to our information request fax dated August 21, 2008, you state to question 1A “The related Kaplan-Meier curve will be identical to Figure 11.1.1 of the clinical study report for the primary analysis variable if restricted to the 4 hour period ...” Thus, it appears that the analysis method you described in Amendment 17 was the same method used for the primary endpoint analysis that was to have been done according to the protocol, except that

our August fax asked you to impute a value of 4 hours rather than 24 hours for “Subjects receiving open label clinical trial material (CTM) or rescue medication or analgesics or anti-emetics before 4 hours and prior to initial relief of symptoms.” According to the “DEFINE.PDF” document submitted as part of Amendment 17, derived variable, “CMPPFL” is defined to a value of “Y” if concomitant medication is allowed by protocol in the given time window.” Please clarify the time window used to determine values for CMPPFL.

- We note that the variable “SGANAN” (SG [subgroup] with/without analgesics/anti-emit-num”) was assigned a value of “1” if at least one of cmexcl1a, cmexcl2, cmexcl3, -- cmexcl10 = ‘Y’” In the original submission concomitant medication dataset, ADCM, includes the following variables:
 - “CMEXCL1A” is defined as “C1-INH(+FFP) (4hrs)”
 - “CMEXCL2” is defined as “Anti-Emetics: Antihistamins [sic] (<4h),”
 - “CMEXCL3” is defined as “Anti-Emetics: Antidopaminergics (<4h)”
 - “CMEXCL4” is defined as, “Anti-Emetics: Benzodiazepines (<4h post)”
 - “CMEXCL5” is defined as “Anti-Emetics: Corticosteroid (<4h post),”
 - “CMEXCL6” is defined as Anti-Emetics: 5HT Recep. Antag. (<4h),
 - ” CMEXCL7 is defined as, “Anti-Emetics: Miscellaneous (<4h),”
 - “CMEXCL8” is defined as “Anti-Cholinergics (<4h),”
 - “CMEXCL9” is defined as “Narcotic Pain Meds = Analgesics (<4h),” and
 - “CMEXCL10” is defined as “ACE Inhib. Within 4 Weeks Before Treat.”

It is not clear whether you have used derived variable SGANAN is analyses of the study’s primary efficacy endpoint. Please clarify.

- If you have used derived variable SGANAN in primary endpoint analyses, it appears you may not have properly

followed the protocol and imputed values of 24 hours (or 4 hours in the case of analysis 1A requested in our fax information request dated August 21, 2008) for all subjects who received analgesics, anti-emetics, or “non-permitted” medications which may potentially confound interpretation of the primary endpoint only if such medications were first administered prior to the subject’s self-reported time to start of relief of HAE attack symptoms. Please comment.

- It is not clear whether administration of any of the additional 4 classes of medications/medications “Non-permitted” by the protocol until after complete resolution of the HAE attack were taken into account in determining values of the derived variables CMEXCL1A and SGANAN. The additional 4 classes of “Non-permitted” medications/medications included:
 - Any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis
 - Attenuated androgens (for subjects not previously treated with androgens) or increased doses of androgens (for subjects already treated with androgens)
 - Tranexamic acid (for subjects not previously treated with tranexamic acid) or increased doses of androgens (for subjects already treated with tranexamic acid)
 - Aminocaproic acid (for subjects not previously treated with aminocaproic acid) or increased doses of androgens (for subjects already treated with aminocaproic acid)
- We note that a number of subjects received tranexamic acid, plasma protein concentrate, and attenuated androgens during the study, according to the original concomitant medications ACDM database. However, as noted previously the original ADCM database has missing values for variable “TONALG” for a majority of the concomitant medications having analgesic or anti-emetic properties or that were among the list of medications “Non-permitted” by the protocol. During the teleconference held on 12 November with representatives of your firm and Drs. Wang and Pierce and Ms. Valencia of this Office, your representative indicated that you did, in fact,

impute a “poor/failure” outcome of 24 hours for subjects who received any of the 6 classes of medications “Non-permitted” by the protocol, including tranexamic acid, etc.

However, inspection of Appendix IVb: “Impact of Concomitant Medications and Rescue medication on PP- and sub-population definition and on primary efficacy variable” suggests that the administration of androgens, “transexamic” [sic] acid, “aminocarproic” [sic] acid and “Any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis [other than FFP]: was not taken into account in the calculation of the key variable, “TtRel⁺” (also variously called “TTRELP” and “TTREL+”), which was defined according to your DEFINE.pdf document as “Time to relief of symptoms with p/f ass.” and “TTRELP = TTREL with poor/failure assessment: TTRELP = 24 if use of analgesics or rescue medication before start of relief nor no relief was reached otherwise TTRELP – TTREL” Please clarify.

- Please clarify whether TTANA (“time to analgesics”) and TOANALG include data for masked rescue study medication (including placebo), as this is not clear from your derived variable definitions.
2. Please provide a single analysis database that contains all raw data and derived data fields needed to completely validate your primary efficacy endpoint of time to initial relief of symptoms.
 3. Please indicate the date the blind was broken for phase II/III study CE1145_3001 (IMPACT I).
 4. Please indicate the date that the revised statistical analysis plan version 2.0 dated October 26, 2007 (approximately 1 month before the last subject completed the day 7-9 follow-up) was submitted to the IND.
 5. Please provide a written table and analysis database that lists all subjects for whom, in the protocol-defined primary endpoint analysis, you have imputed a poor/failure value of 24 hours. Include for each subject in the table the specific reason for imputation of the poor/failure value of 24 hours (i.e., analgesic drug administered at 3.0

hours, which was prior to TTREL value of 3.5 hours; missing TTREL, etc.)

6. We request you redo the primary endpoint analyses for the ITT population taking the following into account:
 - The protocol stated “Concomitant medications should be kept to a minimum during the study, especially during the acute attack. However, if these are considered necessary for the subject’s welfare and will not interfere with the study medication/study endpoint, they may be administered at the discretion of the investigator...Due to potential interference with assessment of the primary efficacy variable, the use of pain medication and anti-emetics is strongly discouraged during the acute phase of treatment. If possible, these medications should not be used until at least four hours after start of study medication administration. **Subjects will be counted as non-responders regarding the analysis of the primary endpoint, if they have received these types of medications listed in the CRF.**”

We note, however, that the use of discouraged and “non-permitted” (open-label C1-Inhibitor, fresh-frozen plasma, etc.) during the study was extensive. By our count, using the original submission ADCM concomitant medications database, at least 65 out of 124 (>50%) of randomized subjects received “discouraged” or potentially “non-permitted” medications during the study.

In order to understand the impact of the administration of these concomitant medications on the study outcome measures, we need to know when these medications were administered in relation to variables such as ToSRel (time of initial relief of symptoms) “TTREL” (time of initial relief of symptoms minus time of administration of randomized CTM) and the derived data variable, “TTRELP” (also variously called TTREL+ and TtRel+ in your BLA and various amendment submissions, corresponding to TTREL, but set to a “poor/failure” imputed value of 24 hours in the case of subjects who received rescue study medication or open label CTM or analgesics or anti-emetics or FFP prior to TTREL).

- Given that the protocol specified to count as treatment failures subjects with missing data for time to initial relief of symptoms, we request you classify subjects who received concomitant medications with analgesic or anti-emetic pharmacologic

properties prior to time to initial relief of symptoms as having poor/failure outcomes for the primary endpoint and impute a value of either 24 or 4 hours for time to initial relief of HAE attack symptoms, depending on the particular primary endpoint analysis.

- We request you also impute a “poor/failure” outcome of 24 or (or 4, depending on the analysis) hours for all subjects who received any of the 6 categories of medications/medications “Non-permitted” by the protocol (i.e., “any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis, fresh frozen plasma (FFP), attenuated androgens, tranexamic acid, or aminocaproic acid (for the latter 3 drug classes only if the subject was not previously treated with the drug or if previously treated but administered increased doses of the drug) either within 5 hours prior to the time of administration of randomized CTM or prior to TOSREL (time of start of relief of symptoms) or for whom the start date and/or time of such concomitant medications is missing.
- In amendment 16 you state on p 6 in partial response to our request 4 of our 21 August 2008 fax that “In the concomitant medication dataset ADCM the variable TOANALG (time of start of analgesics/anti-emetics/C1 INH/FFP concomitant medication) is filled with the start date of the medication if the medication is on the list of analgesics/anti-emetics/C1 INH/FFP. In all other databases TOANALG contains the first start date of an analgesics/anti-emetics/...concomitant medication within a subject.” Your representative indicated during the teleconference held 12 November 2008 that the list of analgesics/anti-emetics/C1 INH/FFP” was contained in an appendix to the [revised] statistical analysis plan. Incidentally, we note that this list was not included in the original statistical analysis plan, but was submitted approximately 1 month before the last subject had completed the 7-9 day follow up visit of the study. Appendix IV: “Prohibited medications, StatusOctober26, 2007” lists “Narcotic Pain Medications (Analgesics)” but does not include non-narcotic analgesics, such as non-steroidal anti-inflammatory agents (NSAIDs) or acetaminophen which could, for example confound the interpretation of the response of HAE attack symptoms of facial tightness, abdominal discomfort, etc. The protocol stated on p 21 under the heading “Pain medication and anti-emetics” “Subjects will be counted as non-responders regarding the analysis

of the primary endpoint, if they have received these types of medications listed in the CRF.” On p 35 of the protocol under section 7.3.1 (Analysis of efficacy – Primary efficacy criterion) it states that “Then the primary efficacy variable is defined as:

- (i) $TtRel+ = 24$ hours (poor/failure outcome), if
 - the subject has received rescue study medication before $ToSRel$ was reached
 - the subject has received analgesics/anti-emetics before $ToSRel$ was reached,
 - $-ToSRel - ToS > 24$ hours,
Or $ToSRel$ cannot be determined because of missing values
- (ii) $ToSRel - ToS$, otherwise

[where ToS = Time of start of study treatment and
 $ToSRel$ – time of start of relief of symptoms]

We therefore request that you add non-narcotic analgesics, including NSAIDs and acetaminophen, to the list of “any rescue medication” that results in an imputation of a “poor/failure” value of 24 (or 4, as appropriate, depending on the analysis) hours for subjects who were administered such concomitant medication anytime from 5 hours prior to ToS up to $ToSRel$ (time of start of relief of symptoms). Please redo and resubmit your primary endpoint analyses accordingly.

- When you redo and resubmit your analyses of the primary endpoint, please use the actual times of administration of “any rescue medication” (including all “discouraged” and all 6 classes of “Non-permitted” medications) as indicated on hospital record source documents to impute values of 24 (or 4, as appropriate, depending on the analysis) hours for subjects who received any such concomitant medications within the time frame from 5 hours prior to the time of administration of randomized CTM to “ $TOSREL$ ” (time to initial relief of symptoms) and imputing a value of 24 or 4 hours, as appropriate, for any subjects with missing data for date/time of administration of such medications.
- We note that 9 subjects are listed in the original submission ADCM concomitant medication database as having received “C1-INH” or “Berinert” and this is less than the total number of

subjects in the study who received masked (blinded) rescue study medication as listed in Table Q1c (24 in the placebo group, 13 in the Berinert 10 U/kg group, and 8 in the Berinert 20 U/kg group). Please clarify whether you imputed a “poor/failure” value of 24 (or 4, depending on the analysis) hours for all subjects who received any C1-Inhibitor product within 5 hours prior to the time of randomized CTM administration or prior to TOSREL (time of initial relief of symptoms), whether recorded as concomitant medication or as rescue study medication. When you resubmit the primary endpoint analyses requested above, please impute a “poor/failure” outcome of 24 (or 4, as appropriate, depending on the analysis) hours for subjects who had any C1-Inhibitor listed on the CRF but for whom the start date and/or start time was missing.

7. In the original submission efficacy database, the field heading “SGANA” is defined “SG [subgroup] with/without analgesics/anti-emet/C1.” We note that among the 65 or more subjects who received “any rescue medication” by our count in the original submission concomitant medication database ADCM, that only 4 subjects (Nos. ---b(6)-----) are listed as “with” “analgesics/anti-emet/C1.” Please explain this discrepancy.
8. In the original submission efficacy database, the field heading “SGRECS” is defined “SG [subgroup] with/without any rescue medication.” We note that among the 65 subjects who received “any rescue medication” by our count in the original submission concomitant medication database ADCM, that 37 subjects were incorrectly classified as not having received “any rescue medication. Among the “discouraged” or “non-prohibited” medications these subjects received were morphine, Demerol, phenergan, and odanasetron, among others. Please comment.
9. It does not appear that you provided the requested analysis 1C of the breakdown by randomized treatment group of the use of “any rescue medication” as requested in our fax to you dated August 21, 2008, which did not restrict the time frame of administration of such potentially confounding concomitant medications. Please submit analyses in response to question 1C that
 - (a) include all medications covered by “any rescue medication” anytime from 5 hours prior to ToS (time of start of study treatment) through day 7-9 of follow-up and

(b) include all such medications administered from 5 hours prior to ToS through time to complete relief of symptoms.

10. In amendment 16 submitted September 3, 2008 in response to our August 21, 2008 information request item 1C, you cited Table 10.5 in supportive of the first bullet in your reply to our request for the analysis of “The proportion of subjects in each randomization treatment group that received open label CTM or rescue medication or analgesics or anti-emetics in each randomization group.”

This table shows a total of only 4 subjects across the 3 randomization groups who received analgesics/anti-emetics/C1-Inhibitor as concomitant medications.

This total would seem to conflict with the revised information on the use of concomitant medications presented in the safety update, which strongly suggests that the actual number of subjects who received such concomitant medications was larger than 4.

Please provide a printed table and an analysis database with the subject ID numbers, TTREL, TTRELP, time to complete relief of symptoms, the difference between the time randomized CTM is administered and the start data and time of open label CTM or blinded rescue medication or analgesics or anti-emetics were given (irrespective of whether they were begun before or after initial relief of symptoms). **Consistent with the protocol-defined primary endpoint analysis, please include all drugs/therapeutic agents that have analgesic or anti-emetic pharmacologic properties, regardless of whether you have previously classified them as analgesics or anti-emetics.** This will include, but not necessarily be limited to the following concomitant medications in addition to open label or masked CTM, as taken from your safety update: medications you have classified as:

- analgesics (4/42 placebo subjects, 4/39 Berinert 10 U/kg subjects, and 2/43 (4.7%) of Berinert 20 U/kg subjects),
- fentanyl (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 0/43 of Berinert 20 U/kg subjects),
- ibuprofen or ketorolac tromethamine (1/42 placebo subjects, 2/39 Berinert 10 U/kg subjects, and 1/43 (%) of Berinert 20 U/kg subjects),

- vicoprofen (1/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 0/43 of Berinert 20 U/kg subjects),
- ASA (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 0/43 of Berinert 20 U/kg subjects),
- prednisone (0/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects),
- promethazine (2/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 2/43 (4.7%) of Berinert 20 U/kg subjects),
- hydroxyzine (1/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects),
- plasma protein fraction (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects), and
- medications you have classified as antiemetics/antinauseants (1/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects).

We note that you separated into several different pharmacologic classes drugs which have analgesic properties.

11. Although the cover letter to Amendment 17 dated 12 September 2008 states “The purpose of this submission is to supply a complete response to item 1, it is unclear from inspection of Attachment 3, “Table of Contents for PDF documents,” whether such a response was provided, either in the form of a narrative discussion or tables or figures responding to FDA item 1A request.

The requested item 1A analysis from Amendment 17 read as follows:

Kaplan-Meier Curves for the high dose and placebo groups of the primary endpoint through 4 hours with corresponding p value for the difference in Kaplan-Meier curves. The exclusion of data beyond 4 hours avoids the artificial inflation of p values that occurs when a value of 24 hours is assigned to subjects who received rescue medication or open label CTM or analgesics or anti-emetics after 4 hours and prior to initial relief of attack symptoms. Mean and median times to initial relief of symptoms that include imputed 24 hour values and their associated p values should be deleted. Subjects receiving open label CTM or rescue medication or analgesics or anti-emetics before 4 hours and prior to initial relief of symptoms would be assigned an imputed time to initial relief of 4 hours [emphasis added.]

- Table Q1a1.2 is described in your “Table of Contents for PDF documents” of Amendment 17 as “Time to start of relief: Time to start of relief (TrRel+a1) with censoring of subjects at 4 hours who received rescue study medication or open label CTM or analgesics or anti-emetics (before or after 4 hours) Generalized Wilcoxon test and Log-rank test between placebo and Berinert P, Dosage group II (2- U/kg b.w.).” This seems to conflict with with the information at the top of Kaplan-Meier plot Figure Q1a.1, which states it is based on the same derived data field, TtRel+a1. The title of this figure reads “Figure Q1a.1: Kaplan Meier Graph: Time to start of relief (TtRel+a1) with censoring of subjects at 4 hours who received rescue study medication or open label CTM or analgesics or anti-emetics (before or afer 4 hours **but before start of relief**) – ITT population [emphasis added].” Please clarify.
- In addition, item 1 of our 21 August 2008 fax stated “Please describe which specific data fields in which databases may be used to generate the above analyses. If derived data fields have not been provided to permit the direct calculation of the above analyses, please provide them together with a list of expanded data field definitions and the -b(4)- code for calculating the derived data fields.” Your response appears to be incomplete, in that:
 - We note that in Amendment 17 you do not appear to have provided a database to permit verification of your response to requested analysis 1C from our August 21, 2008 information request fax.
 - In Amendments 16, dated 3 September 2008, and in Amendment 17 dated 12 September 2008, it is not clear whether you have provided the derived data field for the difference between the time of blinded CTM administration (ToS) and the start time of administration of prohibited analgesics, anti-emetics, open-label C1-Inhibitor, and masked rescue study medication (see FDA request No. 4 in our 21 August 2008 fax). In your answer to item 4 you discuss TTANA, which is defined as “Time to [sic] between start of randomized CTM to start of analgesics/anti-emetics/C1-INH/FFP concomitant medication in hours.” From this definition it is not clear whether masked CTM (including masked rescue placebo for the 20 U/kg Berinert randomization group) is included in this variable and IN TOANALG in Concomitant Medication database ADCM.

- A derived data field that would include open label C1-INH and rescue study CTM (“all study rescue medication”) as well as analgesics, anti-emetics, and any of the 6 classes of medications “Non-permitted” by the protocol (page 21, section 5.4) and supporting raw data fields showing the time and date of administration of these medications would help us to determine whether you have correctly imputed 24 hour (or 4 hour, as appropriate, depending on the analysis) poor/failure values for the primary endpoint, time to start of relief of HAE attack symptoms for the appropriate set of subjects. This is because only if this time difference equals or is less than TTREL should a poor/failure value of 24 hours be imputed for the primary endpoint, according to the study protocol.
- As noted above, inspection of original submission database ADCM reveals that the majority of subjects who received concomitant medications with analgesic or anti-emetic pharmacologic properties have missing values for their starting date and time. Thus, it is not possible to determine for these subjects whether these subjects should be classified as poor/failure outcomes and whether to impute 24 values for TTREL (TTREL+) for these subjects. Given that the protocol specified to count as treatment failures subjects with missing data for time to initial relief of symptoms, we request you classify such subjects as having poor/failure outcomes for the primary endpoint and impute a value of either 24 or 4 hours for time to initial relief of HAE attack symptoms, depending on the particular primary endpoint analysis.
- In amendment 16 you state on p 6 in partial response to our request 4 of our 21 August 2008 fax that “In the concomitant medication dataset ADCM the variable TOANALG (“time of start of analgesics/anti-emetics/C1 INH/FFP” concomitant medication) is filled with the start date of the medication if the medication is on the list of analgesics/anti-emetics/C1 INH/FFP. In all other databases TOANALG contains the first start date of an analgesics/anti-emetics/...concomitant medication within a subject.” Please clarify whether TTANA and TOANALG are intended to include data for masked rescue study medication (including placebo), as this is not clear from your definitions.

12. From table 11.2.1 it is apparent that 3 placebo subjects received “study rescue medication, and analgesics/anti-emetics/open label C1-INH/FFP between 1 and < 4 hours from when masked randomized study CTM was administered. The table shows an additional subject who received prohibited medication at time zero. Field TTRESC in database ADCM shows only subject --b(6)-- received rescue medication during the time window 0 to < 4 hours (1.67 hours). No value is given for this subject in field TTANA (“Time to [sic] between start of randomized CTM to start of analgesics/anti-emetics/C1-INH/FFP concomitant medication in hours.” From inspection of the field values for TTANA, subject --b(6)-- received the anti-emetic prothiazine at 1.5 hours and subject --b(6)-- received the anti-emetic Phenergan at 3.07 hours.

Please redo table 11.2.1 after assigning “poor/failure” outcome values of 24 (or 4 hours, as appropriate, depending on the analysis) to subjects with missing data for the start date/time of administration of “any rescue medication” and using updated times of administration of “any rescue medication” given between 5 hours prior to ToS until ToSrel as obtained from hospital medication source records.

13. We note that in the concomitant medication database ADCM in the original database, there were a total of 9 subjects listed who received either “C1-INH” or “Berinert” as concomitant medications (subject nos. -----b(6)-----). The study report discusses a single subject who received open-label Berinert during the initial 4-hour period. Please provide a printed table and database listing all subjects who received C1-Inhibitor/Berinert at any time during the trial together with the difference in time between the time zero administration of masked randomized CTM and the administration of C1-Inhibitor/Berinert, TTREL, TTRELp, and time to complete resolution of symptoms. Please discuss the impact, if any, of the administration of C1-Inhibitor/Berinert as a concomitant medication on each study endpoint, including time to complete relief of symptoms.

14. Although Figure 11.2.1 states for Berinert 20 U/kg bw “N-43, censored – 5),” Figure 11.1.1 shows that 6 subjects in this high dose group were assigned [an imputed time] to initial relief of symptoms of 24 hours. Please explain this discrepancy.

15. You state on page 90 in section 12.3.2 in the interim study report for open-label extension study CE1145_3003 (IMPACT II) “As there

were no deaths, no related SAEs, and no other significant AEs, detailed narratives are available upon request since this information does not affect the safety claims made in this report.” Please provide a detailed narrative of the “infusion related reaction” that led to premature discontinuation of administration of Berinert and premature discontinuation from the study. Your study report does not identify the subject number of the individual who experienced this treatment-emergent reaction which was attributed to administration of Berinert or provide any details as to the nature of the “infusion related reaction.”

16. Subject --b(6)-- experienced a severe AE recorded as an exacerbation of hereditary angioedema. This subject received rescue medication on 20 March 2006 at “61500,” according to column “RESCSTTI” in the ADAEFDA database. Please explain the units of the variable field.

17. Please submit a letter to the BLA file committing to:

- Submit a protocol within 120 days of receipt of this letter for conducting a randomized masked study to further evaluate the efficacy of the product in acute facial HAE attacks and to obtain additional immunogenicity data. We recommend the study enroll at least 40 subjects to be randomized to Berinert plus 20 subjects to be randomized to placebo. The study should have adequate power to evaluate the efficacy of Berinert for facial HAE attacks. Unequal randomization should aid enrollment. Subjects should have a history of facial HAE attacks but may be enrolled at the time of their first acute GI or facial HAE attack following screening and may receive open-label Berinert for GI attacks but be randomized to receive either Berinert or placebo for facial attacks. Subjects may receive Berinert as add-on therapy to standard of care, such that analgesics and anti-emetics may be used at the investigator’s discretion at any time. However, we discourage the use of rescue Berinert for facial attacks in order to better understand the time course of subject response to Berinert in facial attacks. Antibodies against C1-Inhibitor should be measured at baseline and after 3, 6, and 9 exposures to the product, or every 3 months, whichever comes first, for a total of 12 months. Subjects with antibodies positive by --b(4)-- should be tested for inhibitory antibodies using a validated assay. The study report should describe in detail attempts to correlate treatment-emergent antibodies with AEs. Efficacy data for GI attacks

need not be collected. The analysis may include more than one facial attack per subject if adequate methods are employed to account for the intra-subject correlation of response.

- Initiate the above immunogenicity/facial attack protocol within 90 days of acceptance by FDA of the final protocol
- Provide within 90 days of acceptance by FDA of the final protocol target dates for (a) completing enrollment, (b) completing the study, and (c) submitting the final study report to the IND as an electronic submission with cross-reference to the BLA. The final study report should be submitted to FDA within 9 months of completion of the study.
- Develop and implement a post-licensure pharmacovigilance plan, per the ICH E2E Pharmacovigilance Planning guidance, to monitor long-term safety with the use of C1-Inhibitor. The major components of a pharmacovigilance plan for C1-Inhibitor should include routine pharmacovigilance (i.e., compliance with applicable post-market reporting requirements under FDA regulations) and additional post-market actions, including a patient registry (see next bullet), to address any potential safety issues, such as the possibility for thrombotic adverse events and/or viral transmission.
- Establish and maintain a patient registry of patients treated with C1-INH for any indication. HAE is a very rare disease, and increased reporting of associated safety problems may be achieved by use of a patient registry. Variables to record as part of the registry include indication for C1-Inhibitor, administered doses, patient demographics, concomitant medications and plasma products, adverse events, including possible thrombotic or embolic events, and results of any viral testing.

REVIEW

Clinical and Regulatory Background

Disease or Health-Related Condition(s) Studied and Available Interventions

Important Information from Pharmacologically Related Products, Including Marketed Product

The product is pooled plasma-derived C1 Esterase Inhibitor (C1-INH), marketed in Europe as Berinert P. The development name is CE 1145. C1-INH is a serine protease inhibitor. Others in this group include alpha 1 anti-trypsin (AAT), alpha2-antiplasmin, and heparin cofactor II, among many others

A NOTE ON OTHER PLASMA-DERIVED C1-INH PRODUCTS.

No C1-INH products are currently licensed in the U.S. for treatment of acute HAE attacks. -----b(4)-----

Lev Pharma C1-Inhibitor product was licensed in 2008 for routine prophylaxis to prevent acute HAE attacks.

MECHANISMS OF ACTION

C1-INH has inhibitory activity on at least 4 human cascade systems:

- **Complment system**
- **Contact/Bradkinin-Kinin system**
- **Fibrinolytic system**
- **Coagulation cascade**

C1-INH inactivates its targets by covalent attachment to the reactive sites. The sponsor suggests that all of the above 4 systems area activated during an HAE attack and contribute to edema formation.

DISEASE

Hereditary angioedema (HAE) is a rare disorder with 3 types characterized by acute episodes of non-pruritic facial, extremity, GI mucosal, GU mucosal, and/or laryngeal edema (LE). While LE is life threatening, the other much more common types of attacks are self limited and treated symptomatically. Type I HAE patients have low concentrations of antigenic and functional C1 esterase inhibitor (C1-INH). In HAE Type II, antigenic C1-INH levels are normal, but functional levels are low due to synthesis of normal amounts of a dysfunctional protein.

C1-INH is a soluble single-chain glycoprotein containing 478 amino acid residues with an apparent MW of 105 kD. Carbohydrate comprises 26 to 35% of the mass of the molecule. It is primarily synthesized in the liver and the native protein has a half-life of 64 hours in normal individuals. The half life in Types I and II HAE is can be reduced to as low as ~ 21 hours.

Both HAE Types I and II are inherited in an autosomal dominant pattern. Overall prevalence of HAE Types I and II combined has been estimated to be 1 in 10,000 to 1 in 50,000 with a greater prevalence of the former type (5:1 to 6:1, est.). HAE Type III is not associated with abnormal C1-INH levels. The edema of HAE attacks is due to acute generation of substances in plasma increasing vascular endothelial permeability.

ALTERNATIVE THERAPIES

No specific therapeutic agents are licensed or approved for treatment or mitigation of acute HAE attacks in the U.S., although a few products are available commercially outside the U.S. -----b(4)-----

Abdominal attacks are treated symptomatically with analgesics and anti-emetics as needed. Many HAE patients, perhaps because of repeated exposure to narcotics, have exhibited drug-seeking behavior. Harrison's Principles of Internal Medicine notes that this fact should be taken into account in the design of studies in this disease.

Several agents have been used to prevent HAE attacks, most notably oral androgens, such as danazol (17beta-hydroxy-2,4,17alpha-pregnadien-20-yno [2,3-]isoxazole). The latter have a variety of possible side effects, many dose related, and may cause virilization in females with prolonged use, especially at higher doses.

Regulatory Background Information (FDA-Sponsor Meetings, Advisory Committee Meetings, Commitments)

See Module 5 – 5.4.149 through 5.4.160 in BLA volume 28 for pre-IND meeting and other meeting minutes and correspondence.

Previous Human Experience with the Product Including Foreign Experience

REVIEW OF FOREIGN POSTMARKETING DATA

Berinert P was introduced into the European Market as a non-pasteurized product in 1979 and then as a pasteurized kproduct in 1986. It was introduced in Japan in 1990 and in Argentina in 2003.

The original BLA was missing foreign postmarketing data for the initial period of European marketing from 1979 to 1999. The original BLA referred to 57 suspected adverse reactions (ADRs) for the period 1985 through December 2007, but did not identify what type of ADRs were received prior to 1999. The sponsor was asked to submit comprehensive cumulative line listings and narrative summaries for all 57 suspected adverse reactions (ADRs) for the period 1985 through December 2007. These data were submitted in amendment 19 on 23 September 2008, and were reviewed both by myself and by the epidemiology part of the CBER Division of Biostatistics and Epidemiology. The sponsor was asked to provide all available details concerning the 4 cases of suspected viral transmission by the product.

Sponsor Response:

The sponsor states that “expected” AEs are those contained in the Company Core Safety Information (CCSI), which is based on the ADRs included in the product information of countries in which Berinert is licensed. Those not included in the package insert [CCSI] are described as “unexpected.”

Overall, 37 of 57 reported ADRs are “expected” using the above definition. These include 5 vases of suspected virus transmission, 14 cases of thrombosis, 7 cases of allergic/anaphylactic reactions, 2 cases of chills and fever, and 9 cases of lack of effect

Attachment 6 of the amendment contains details of the reported ADRs.

Table 1 shows 2 cases of anaphylactic reaction/anaphylactic shock and one of BP decrease to 90/40 in which the causality was assessed by the sponsor as possible.

Table 5 on p 6 of Attachment 6 of the amendment lists 5 cases of suspected virus transmission by the product resulting from spontaneous postmarketing reporting. In each case, the sponsor has rated causality as unlikely. The cases are summarized below.

| <i>Company Case ID</i> | <i>ADR</i> | <i>Serious?</i> | <i>Comment</i> |
|------------------------|--------------------------------|-----------------|--|
| ---b(6)---- | <i>Hepatitis C</i> | <i>Yes</i> | <i>Lot produced from HCV genome negative tested source plasma</i> |
| ---b(6)---- | <i>Hepatitis B</i> | <i>Yes</i> | <i>Product last given 2 years prior to diagnosis. Pt reported "very close contact" with a high-risk population during a trip through Africa which had occurred 2-3 months before the diagnosis of hepatitis B.</i> |
| ---b(6)---- | <i>CMV Infection</i> | <i>Yes</i> | <i>This infection occurred in a 2 month old baby. The reported incubation period was only 1 day. The reporting MD assessed a "connatal" infection as the most probable cause.</i> |
| ---b(6)---- | <i>"HGV" (-b(4)-) Positive</i> | <i>No</i> | <i>This case of hepatitis G seroconversion occurred in an unsponsored study. No other reports of suspected virus transmission regarding the involved lots were obtained, but testing was not described. The sponsor states that the manufacturing process has demonstrated high virus inactivation/ elimination capacity for BVD, a model for hepatitis G.</i> |
| ---b(6)---- | <i>Hepatitis B</i> | <i>No</i> | <i>This female was diagnosed with hepatitis B in 2003 several months after receiving Berinert. Despite queries, no further information was provided. The implicated lot was manufactured from HBV-b(4)- negative source plasma.</i> |

Reviewer Comment:

Regarding hepatitis C, no information is provided regarding risk factors or whether the sponsor attempted to obtain additional data.

Regarding hepatitis B, the first case is apparently confounded by a risk factor in the subject and had a 2 year delay in the diagnosis from last exposure, but there is nothing to rule out the 2nd case except for the negative result with testing source plasma by -b(4)-. It would be helpful if the sponsor distinguished between acute and chronic hepatitis B.

Regarding CMV, the stated delay from last product administration to onset of CMV infection is 1 day, which is too short.

Regarding the hepatitis G case that occurred in a study not sponsored by CSLB, the sponsor notes no other viral seroconversions from the implicated lots, but gives no information as to whether the other subjects in the study were tested for hepatitis G.

Module 2, vol 1 p 48 of tab 2.5 in the clinical summary of the original BLA submission states there were 4 cases of suspected virus transmission from worldwide postmarketing surveillance, out of an estimated --b(4)---- estimated single standard doses of the product sold from 1985 through 2007. This is at variance with the data in the table above reported in amendment 19. The sponsor states that viral transmission is “covered by the known safety profile of CE1145” [because the theoretical possibility of adventitious agent transmission by the product is mentioned in their core safety sheet].

Module 5 (5.4.6.1) contains 2 PSURs (Periodic Safety Update Reports), prepared for the EU, dated Jan 1999 to Jan 2004 and Jan 2004 to Mar 2007, respectively, plus 2 Addendum Reports, which extend the reporting periods of each PSUR (Mar 2007 to Aug 2007, and Aug 2007 to Jan 2008). Previous safety reports exist for the 5 year period Jan 1984 to Jan 1989 and each one year period thereafter until Jan 2001, but are not included in the BLA.

These PSURs and their addenda cover safety data for all forms of administration and all indications of Berinert P. However, no line listings of individual adverse reactions are included for the addenda because no “cases of suspected adverse drug reactions were received.”

During the most recent addendum period, the Mix2Vial was introduced for reconstitution.

Analysis of Postmarketing Adverse Reaction Reports (ADRs)

PSUR Jan 1999 to Jan 2004: 24 reports were received.

A Warning concerning thrombotic events in the setting of high dose off-label use of the product in an attempt to prevent or treat capillary leak syndrom following cardiac surgery under extracorporeal circulation was added to the label in December 1999 and reworded in March 2002.

In total, 14 cases of suspected thrombosis were received, mostly (n = 12) in neonates with congenital heart anomalies. One report was in a 6 year old boy and one in a senior adult subject. The latter received 100 U/kg and experienced basilar artery cerebral thrombosis diagnosed 6 hours following administration of the study medication. Doses ranged from 105 to 926 U/kg in the pediatric subjects and ~ 100 U/kg in the adult subject. Five thrombosis reports were received spontaneously from 1998 to 2001 and 9 further reports were actively collected during inquiries with reporting centers.

Reviewer Comment: Because of the known risk of thrombosis at higher doses of Berinert, and no data to define the lowest thrombogenic dose, plus the potential for off-label use at higher doses, the sponsor is urged to create and maintain a registry of subjects who receive Berinert in the U.S. for any indication (See RECOMMENDATIONS).

PSUR Jan 2004 to Mar 2007: 11 reports received, of which 7 were serious, including 2 fatal events, and 4 non-serious. No literature reports of unlisted ADRs were received during this period. **One suspected case of hepatitis B virus transmission (#---b(6)----) occurred during this period that was diagnosed several months after the patient had received the product in January 2003. “Despite inquiries, no further information was provided.** A causal relationship to Berinert P was excluded because the respective lot was manufactured from HBV negative source plasma.”

Other listed AEs included 3 allergic-anaphylactic reactions, 1 rise in temperature, and 2 lack of effect. Unlisted ADRs reported during the period included 1 basilar artery thrombosis (#---b(6)----), 1 vertigo, 1 unspecified cause of death, and 1 case of pain on injection. One subject for whom tachycardia and flushing were reported as an allergic event had a positive rechallenge. The sponsor concluded that case ---b(6)---- of anaphylactic shock was possibly related to administration of Berinert P.

The case of **basilar artery thrombosis** involved a 53 year old male with a history of nicotine and alcohol abuse who received 500 U Berinert P for suspected HAE and recurrent urticaria in 2006. He was also being treated with cortisone and antihistamines. He had seizures before and during administration of Berinert P. Six hours following Berinert P he was diagnosed with basilar artery thrombosis and was treated with fibrinolytic therapy. He died approximately 6 days later. An autopsy demonstrated cerebral edema, cerebromalacia, subarachnoidal hemorrhage, brain stem hemorrhage, and basal cerebral [sic, cerebral?] artery sclerosis. No basilar artery thrombosis was seen. It was concluded that the clot lysis therapy had caused cerebral hemorrhage. The sponsor excluded a causal relationship to

Berinert P because only 6 hours elapsed between its administration and the diagnosis of basilar artery thrombosis [Reviewer: on what basis? However, I agree the thrombolytic therapy, perhaps in combination with Berinert P, plausibly caused the cerebral hemorrhage which likely killed the patient].

Two cases of lack of response to the product both involved patients who were receiving ACE inhibitors, which are known to increase bradykinin levels. One of these cases died the day following administration of Berinert P, a 95 year old male with a history of bronchopneumonia, asthma, MI, hyperthyroidism, phlebitis, and PE. It is unclear whether any of these other medical problems were active at the time he received Berinert P.

The latter PSUR also describes briefly a retrospective case collection by --b(4)----- (2006) in which 20 mothers received repeated doses of up to 3500 U per attack during 33 deliveries of 34 newborns. No AEs were reported for any subjects or their babies.

Literature experience

Bork et al published in 2005 data from 75 HAE subjects who had 4834 abdominal attacks treated with C1-INH and compared the results to 17,444 untreated attacks in the same subjects. The number of attacks treated with 500 U was 315 and 1428 were treated with 1000U. Ninety-one attacks were treated with more than 1000 U (maximum of 2000 U). “No drug related adverse events were observed when the injections were performed correctly.” There were reportedly no virus transmissions for HBV, HCV, or HIV.

Kunshak et al. NEJM 1998

Exposure:

Jan 1999 to Jan 2004: Sales of -b(4)- million U worldwide.

Jan 2004 to Mar 2007: Sales of -b(4)- million U, corresponding to --b(4)-- standard doses, according to the sponsor.

Mar 2007 to Aug 2007: Sales of -b(4)- million U worldwide.

Aug 2007 to Jan 2008: Sales of -b(4)- million U worldwide.

Clinical Data Sources (both IND and non-IND), Review Strategy and Data Integrity

BLA/NDA Volume Numbers Which Serve as a Basis for the Clinical Review

Modules 1, 2, and 5. Amendments in response to clinical and statistical fax information requests and teleconferences with the sponsor, including Amendments 6, 7, 10, 12, 13, 17, 18, and 19 and the safety update submitted 19 June 2008.

Literature

See Prior Human Experience Section

Post-Marketing Experience:

See Prior Human Experience Section

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 Berinert 10 U/kg Berinert 20 U/kg | 125 | HAE | Single administration With optional blinded si rescue dos |
| CE1145_3003 | Any HAE attack | Open Label, un-controlled | Berinert 20 U/kg | 39 as of June '07 | HAE | Ongoing |
| 7MN-401CI-OB 7MN-402CI-OB | HBV safety | Open Label, un-controlled | CI-INH 500-1000U IV | 9 4 | HAE, Hered. Or acquired | Single dos 10-16 mo |
| 7A-202CH-B | Post-op Hemodynamics | R, DB, PC | CI-INH 3500 U, 1.1% HSA | 15 per Group | Extra Corporeal Circula-Tion | Single dos |
| 7B-201CH-C | Post-op Performance | R, DB, PC | CI-INH 2500 U, 1000 U 1.1% HSA | 15 per group | Extra Corporeal Circula-Tion | Single treatment scheme |
| 7D-201CI-OB | Efficacy, Tolerance | Open label, un-controlled | CI-INH 500 – 1000 U per dose | 7 | HAE | 1-5 injecti per subjec |
| CE-1145_6001 | Efficacy, Safety | Retrospective Case Collection | CI-INH 500-1000 U/dose | 20 | Pregnant with HAE | 3-10 mont during pregnancy |

Review Strategy

The review focused on the pivotal phase II/III study, CE1145_3001, and to a lesser extent on review of safety data from foreign postmarketing experience and from extension study CE1145_3003. Key elements of the medical review involved noting from review of selected subject case report forms (CRFs that the time to initial relief of symptoms for abdominal HAE attacks in the pivotal study often seemed to be at variance with the time course of severity changes in

individual GI symptoms. This led to a request for the sponsor to reformat the results of the primary endpoint, self-reported time to initial relief of symptoms to that they were depicted in a visual display side-by-side the self-reported intensity scores for individual HAE symptoms on a single page per subject. Based on these sheets, a --b(4)----- database was manually created by me in a masked fashion of time to initial reduction by at least 1 severity category (none, mild, moderate, severe) in which the decrease was required to persist at the following time point assessment and no other GI symptom was permitted to have increased in intensity. The CBER biostatistician then joined with the sponsor's -b(4)- efficacy database so that an analysis of time to initial reduction in any individual GI symptoms by treatment group could be performed. The same robustness analysis was performed for self-reported facial symptoms and for objective masked DSMB ratings of changes in facial photographs that were taken at baseline and hourly. These manually-generated FDA databases of individual HAE symptoms and facial photographs were also analyzed for time to complete relief of symptoms and compared to the sponsor's analysis of the patient's self-reported time to complete relief of symptoms.

The review team endeavored to validate the sponsor's primary endpoint analyses of time to initial relief of symptoms using the ITT population. The primary endpoint analysis is complex because it depends not only on the subject's self-reported time to initial relief of symptoms, based on 2 consecutive "yes" answers to a standard question taking into account all HAE attack symptoms, but also on whether the subject received "discouraged" (analgesics or anti-emetics) prior to self-reported time to initial relief of symptoms, or masked (blinded) study rescue medication (either Berinert or placebo) in which case the protocol required a "poor/failure" outcome of 24 hours was to have been imputed. In addition the sponsor assigned a "poor/failure" outcome to subjects who received "Non-permitted (open label C1-Inhibitor, FFP, etc) medications prior to self-reported time to initial relief of symptoms. Because of ambiguities in the sponsor's definitions of various variable field names in the databases, CBER requested an analysis-ready database containing all derived variables needed to validate the primary endpoint analysis, but using an imputed value of 4 hours for subjects who received "any rescue medication" (including open-label Berinert, analgesics, anti-emetics, or study rescue medication) prior to initial relief of HAE attack symptoms. Because of extensive missing data for the start time and date of a large number of "discouraged" and "Non-permitted" concomitant medications, the "analysis ready" datasets submitted with amendment 17 were found unsuitable for validating the primary endpoint. This was communicated to the sponsor during teleconferences held 10 and 12 November 2008. In addition, the original concomitant medications database was examined by me for medications having analgesic or anti-emetic properties, as well as instances when "Berinert" or C1-INH were administered as concomitant medications. I created an Excel spreadsheet of these potentially confounding medications and the CBER biostatistician joined it with an efficacy database after importing it into --b(4)---. Approximately 1/2 of all study subjects received "any rescue medication" and it was noted that the sponsor had not included NSAIDS or acetaminophen in the "analgesics" or "pain medications" it had used to impute "poor/failure" outcomes for patients who may have received

such medications prior to self-reported time of initial relief of symptoms. _

Good Clinical Practices (GCP) and Data Integrity

The BioResearch Monitoring (BiMo) memo summarizing the findings at the pivotal phase II/III clinical trial study site inspections was received on 3 November 2008. The countersigned memo concludes that the BiMo inspections of three clinical investigators did not reveal any problems that impact the data submitted in the Biologics Licensing Application (BLA).” The inspections were conducted at three clinical sites and represented 32% of the total subjects enrolled in the study submitted in the BLA. The data audit portion of the inspection focused on the verification of the study data on safety and efficacy endpoints submitted by the sponsor in the BLA for all the enrollees at two of the inspected sites (Centers #6 and #8) and for about 50 % the total number of enrollees at Center #12 that were randomly and equitably selected from the total enrollees.” Centers inspected were at Creighton University in NE, the Allergy Clinic of Tulsa in OK, and the Family Allergy and Asthma Center in Atlanta, GA. The main finding was in regard to all 9 subjects at center 8 having a delay beyond the maximum permitted by the protocol (5 hours) between onset of attack and start of randomized masked treatment, as well as a lack of documentation regarding attack starting time. The BLA reports the time between start of attack and administration of randomized test product or placebo exceeded the 5 hour limit in 5 Of 9 subjects at Center 6 and 15 of 22 subjects at Center 12.

Financial Disclosures

Box 1 is checked on Form FDA 3454 and signed by Rainer Maria Schultz on 12 Feb 2008. A 10-page list of investigators and their sub-investigators is attached for study sites 02 through 132.

Human Pharmacology (Immunogenicity, Pharmacology, Pharmacokinetics

See Clinical Pharmacology Review and Clinical Section.

CLINICAL STUDIES

CLINICAL DEVELOPMENT

The sponsor took into account several CBER recommendations in designing (1) a pivotal prospective, multinational, randomized, parallel-group, placebo-controlled, dose-finding, 3-arm, double blind phase II/III clinical

trial to be conducted in the U.S., Canada, and Europe (study CE1145_3001) and (2) an historically controlled trial in -----b(4)-----
----- . The latter trial was never initiated. The sponsor went against CBER's advice in including in the pivotal study _3001 population both subjects with abdominal attacks and subjects with facial edema attacks. The latter would not be expected to result in hospitalization unless accompanied by other severe symptoms, such as intractable abdominal pain or laryngeal edema. Having decided to include both abdominal and facial edema attacks in the trial, the sponsor also declined to follow CBER advice to use the blinded objective evaluation of the resolution of facial edema from 3rd-party examination of coded serial photographs as the component of the primary endpoint related to resolution of facial edema. The sponsor did agree, however, to limit the percentage of subjects enrolled into study _3001 who had only facial edema to no more than 30 % of subjects enrolled. During the IND phase, the sponsor proposed to change the protocol by allowing inclusion of subjects with peripheral attacks. CBER medical and biostatistical staff consulted among themselves and determined this change, which would have affected the primary endpoint of the study, was unacceptable. The sponsor received word from the DSMB after the originally planned interim analysis that, based on the interim analysis, the study was underpowered and that the low dose Berinert 10 U/kg group showed a trend of inferiority with respect to the higher dose Berinert 20 U/kg group. The DSMB recommended increasing the size of the study 4 fold, to 100 subjects per treatment group. Following a series of consultations with FDA, the sponsor submitted version 6.0 of the protocol on 27 June 2007 which stopped enrollment in the low dose Berinert arm, added an additional interim analysis and a final analysis after 42 subjects had been studied in high dose and placebo arms. The planned number of centers was also increased from 30 to 45 in the U.S., Canada, Australia, Latin America, Israel, and Europe.

PIVOTAL TRIAL in facial edema and/or GI HAE attacks [Additions from protocol amendment 03 submitted 27 June 2007 as IND amendment 45 and prior amendments are underlined; deletions are represented by ~~strikeout~~.]

PROTOCOL No./TITLE: CE1145_3001 Human pasteurized C1 esterase inhibitor concentrate (CE1145) in subjects with congenital C1-INH deficiency and acute abdominal or facial HAE attacks.

PHASE OF INVESTIGATION: III [Protocol states II/III]

COORDINATING INVESTIGATORS:

Per IND:

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OBJECTIVES**PRIMARY**

- To show that 20 Units/kg of pasteurized C1-INH concentrate (Berinert P) shortens the time to onset of relief of symptoms of abdominal HAE attack compared to placebo.

SECONDARY

- To compare efficacy of 2 different dosing schemes of Berinert P in abdominal HAE attack compared to placebo.
- To compare the safety of Berinert P in subjects with HAE between treatment groups.

DESIGN SUMMARY

The completed phase III trial is multinational, prospective, randomized, DB, parallel, PC (normal saline), 3-arm, dose-finding

involving 45 centers, with a revised targeted enrollment of 42 subjects per group (25 in group 1, although 42 were actually enrolled in the low dose Berinert Group) with C1-INH deficiency having an acute moderate to severe abdominal or facial attack. At least 70%/treatment group are required to suffer from abdominal attacks. Only one attack per subject was to be analyzed. Subjects were randomized 1:1:1 using an adaptive randomization method to receive either Berinert P 10 U/kg, 20 U/kg, or saline placebo as a single slow IV injection or infusion. Late in the trial, following discussions with FDA and the DSMB following the interim analysis, the low dose group ceased enrolling new subjects. The DSMB had informed the sponsor that the interim analysis had demonstrated less favorable results in the low dose group vis-à-vis the high dose group. FDA Biostatistics determined no alpha penalty was spent in this initial interim analysis, which was designed to permit sample size adjustment but not premature trial conclusion in the event that efficacy had been shown.

Time to the start of abdominal pain relief, as determined by the subject, a subjective endpoint, is the primary endpoint and was to have been analyzed by a Wilcoxon rank test. A similar endpoint was used in a NEJM publication of a different C1-INH product several years ago and consultants to the sponsor favored this subjective primary endpoint. In order to assess time to initial relief of symptoms, the subject was asked at pre-specified times in relation to administration of study test product, “Taking into account all of the symptoms you experienced with this HAE attack, are you confident that it is starting to improve?” An affirmative answer at 2 consecutive time points was required to score a primary endpoint time to initial relief of symptoms, using the time of the first affirmative answer. A number of secondary and additional efficacy variables were used in the trial, including time to complete relief of symptoms. In many instances (40% of subjects with GI attacks), an analysis of changes from baseline in individual GI attack symptom intensity ratings (none, mild, moderate, severe) compared to the primary endpoint revealed differences. Discrepancies were also noted between ratings for individual GI symptoms and self-reported time to complete relief of symptoms.

Viral safety follow-up testing at 3 months was mandated by the protocol, but these data are missing in the original BLA submission. A DSMB monitored study safety and recommended increasing the study size 4-fold, based on the results of the first interim analysis.

The sponsor did not follow this advice, but rather elected to limit the study to 42 subjects in the high dose and placebo groups and negotiated with FDA to add additional interim analyses and an alpha spending plan. The primary analysis was based on the ITT population. Subjects are to be counted as non-responders regarding the analysis of the primary endpoint, if they have received rescue medication prior to 4 hours or prior to indicating initial relief of symptoms has been achieved. For primary analysis purposes, if a subject received rescue medication after the 4 hour time point but before initial relief of symptoms was reported, the time to initial relief of symptoms was assigned a value of 24 hours. This imputation of time to initial relief of symptoms of 24 hours for subjects receiving rescue medication needs to be taken into account when examining mean or median times to initial relief of symptoms. Had some other time to initial relief of symptoms been imputed for subjects receiving rescue medication, the reported mean and median times to initial relief of symptoms would have been different, as would the magnitude of the between-group differences. Open label Berinert P 20 U/kg could be given for laryngeal edema at any time.

PROPOSED NUMBER OF SUBJECTS: 109 (25 in 10U/kg and 42 in 20 U/kg and placebo randomization groups)

Products mandated by the protocol: Normal saline placebo, Berinert C1-Inhibitor at the randomized dose of either 10 or 20 U/kg.

INCLUSION CRITERIA

- M or F ≥ 6 years of age
- Documented congenital C1-INH deficiency with functional or immunogenic C1-INH level and C4 antigen below the lower limit of the local laboratory reference range (to be confirmed by the central laboratory).
- Documented history of abdominal attacks.
- Acute moderate/severe ***abdominal or facial edema attack*** with duration not longer than 5.0 hrs at the time of infusion with study medication. Only attacks necessitating hospital admission and administration of medication are to be considered moderate/severe.
- Written informed consent.

EXCLUSION CRITERIA

- Life expectancy < 6 months
- Incurable malignancies with metastases
- History of hypersensitivity to study medication
- Acquired angioedema (e.g., onset at age > 40 yrs, no family history, no known HAE mutation [or low C1q level, according to the submission])
- Abdominal pain caused by other pathology (e.g., appendicitis, MI)
- End-stage liver disease (i.e., Child-Pugh score B or C)
- HIV positive
- Increased body temperature > 38 deg C.
- Increased WBC > 12K [changed to > 20K, according to the submission]
- Pregnant, breast feeding, or with intentions to breast feed.
- Treatment with another investigational drug within past 30 days
- Treatment with any C1-INH concentrate within the previous 7 days.
- [Treatment with FFP or native plasma within 7 days of start of study drug treatment, according to the submission.]
- Treatment with ACE inhibitors within the previous 4 weeks.
- [Use of] narcotic pain meds and/or anti-emetics between start of attack and enrollment (signing of informed consent).
- Evidence of narcotic seeking behavior and/or drug addiction (including EtOH abuse).
- Mental condition rendering the subject or his/her legal representative unable to understand the scope, nature, and possible consequences of the study.
- Prior inclusion in the study.

DESIGN/EVALUATIONS/MONITORING

Subjects on prophylaxis (e.g., androgens, tranexamic acid, aminocaproic acid) could be included in the study but the doses of these medications were not to change during the trial.

Subjects were to be randomized 1:1:1 to receive up to two IV injections/infusions (including a single optional “rescue” infusion that could be administered “in the exceptional case” in response to subject and physician assessment 4 or more hours after the original infusion) of CE1145 (Berinert P) at 50 U/mL reconstituted solution or placebo for their attack of abdominal pain as follows.

| Treatment Group | First Infusion (Dose for acute treatment; | Possible second infusion after 4.0 |
|-----------------|---|------------------------------------|
|-----------------|---|------------------------------------|

| | study medication) | hours (Rescue medication) |
|---------|-------------------|---------------------------|
| Group 1 | 10 U/kg | 10 U/kg |
| Group 2 | 20 U/kg | Placebo |
| Group 3 | Placebo | 20 U/kg |

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Study drug must be administered within 5 hours of the onset of the attack and within 90 min after randomization. The infusion rate was 4 mL/min IV.

An adaptive randomization scheme [SAP Appendix 16.1.9.20.2] was used and carried out centrally in order to reduce the chance of imbalance in attack type and treatment group within each center.

The sponsor states no emergency unblinding of study medication occurred during the trial; however there were 3 open label administrations of the study product during or before the initial 4 hour observation period planned to follow the administration of blinded study drug.

“Rescue dosing” will be performed as follows:

“In the event no or only insufficient relief of symptoms has been achieved with the study medication within 4.0 hours after start of infusion (as assessed by subject and physician), there is the possibility in the exceptional case of continued clinical need to administer a second infusion with either active study medication (Berinert P) or placebo.

The same schedule of assessments was to be made for at least 4 hours following [each] use of blinded rescue medication as was to be made during the initial 4 hour observation period.

In the rare case of life-threatening laryngeal edema developing after inclusion into the study (concomitant or subsequent to the abdominal attack), immediate open-label Berinert P treatment was allowed.

Due to potential interference with primary endpoint assessment, use of pain medication and anti-emetics was strongly discouraged during the acute phase/initial 4 hour post-test-product observation period.

Study drug was to be prepared by the local pharmacist to preserve masking. “The volume to be administered will always be adjusted to the volume that would be needed to give 20 U/kg b.w. (the total volume will be split into several syringes, there will be no dilution necessary for smaller volumes). The calculated volume will always be rounded to full mL. Rescue medication (2nd dose) will also be prepared by the study pharmacist to preserve masking. The infusion rate was 4 mL/min IV.

If abdominal pain has not improved within 4 hours after the start of study medication, performance of an abdominal ultrasound is recommended. If abdominal pain has not improved within 6 hours after the start of study medication, performance of KUB x-ray “may” be performed to rule out other causes of abdominal pain.

EFFICACY

See analytical plan. Subjects were to be queried using standard questions at fixed time intervals after starting study medication, but in some cases, queries were skipped at some protocol-specified time points, such as when the subject was asleep.

Facial edema photos were to have been taken at screening, baseline, q 1 hr after start of treatment, at start of relief, at 16 hr and 20 hr after start of tx (the latter if edema still present), and at resolution, but subjective assessment of facial attacks by the subject is the basis of the primary endpoint for subjects with facial edema attacks only. The subject will take digital photos at home if discharged; otherwise the physician or delegate takes digital photos. Photos were assessed by the DSMB, whose members will be blinded to treatment, center and other outcome measures, but this DSMB review of photographs was not discussed in the sponsor’s study report and the sponsor has been asked for the location of these data. Changes from baseline in

photographs were to have been assessed as no change, better, or worse.

EFFICACY-RELATED ANALYTE TESTING

C1-INH and C4 blood levels were to be tested by the central lab at screening, baseline, 4, 8, 12, and 24 hours after study medication, and at week 12. In addition, C1-INH levels were to be tested at 1 hour after study medication.

SAFETY

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.

Visits will occur following discharge at day 7-9 and at week 12 (the latter for viral safety and SAEs only)

Serum amylase

CBC baseline only!

Routine serum chemistries were not obtained as part of this study!

Urinalysis baseline only

Serum troponin baseline only

ECG at baseline only

Serum anti-C1-INH antibodies were not requested in the protocol, but were done on Canadian site subjects (n = 5).

Diary cards were used to record complete resolution of attack, concomitant meds through day 7-9, and any Aes through day 7-9.

CONCOMITANT THERAPY

“Concomitant medication should be kept to a minimum during the study, especially during an acute attack. If they are considered necessary for the subject’s welfare and will not interfere with the study medication/study endpoint, they may be administered at the discretion of the investigator.”

Pain medication and anti-emetics:

“Due to potential interference with assessment of the primary efficacy variable, the use of pain medication and anti-emetics is strongly discouraged during the acute phase of treatment. If possible, these medications should not be used until at least 4.0 hours after start of ~~infusion with the~~ study medication administration.

“Subjects will be counted as non-responders regarding the analysis of the primary endpoint, if they have received these types of medications listed in the CRF.”

Non-permitted meds:

- “Any approved or experimental drug targeting the biological mechanism of action of C1-inhibitor such as modulation of components of the contact or complement system, coagulation, and fibrinolysis.”
- FFP
- Attenuated androgens (for subjects not treated with androgens) or increased doses of androgens (for subjects already treated with androgens)
- Tranexamic acid
- Aminocaproic acid

All “relevant” treatments being taken by the subjects prior to and on entry to the study and all concomitant meds are regarded as concomitant meds and must be document.

PREMATURE DISCONTINUATION

A DSMB consisting of “at least” a statistician and a clinician independent from the sponsor and the study and a Steering Committee appointed for the study may also discontinue the study, or discontinue one of the dosing groups.

Subjects found to have either an acquired angioedema after enrollment, to have other causes for abdominal pain, or who have positive toxicology screening for opioids will be excluded from the efficacy analysis and replaced with a subject receiving a new subject ID number, but will not be excluded from further safety tests, or from safety analyses.

ANALYTICAL PLAN

PRIMARY ENDPOINT

- *Time between start of study medication administration and onset of relief of symptoms from evaluated abdominal or facial attack determined by subject's assessment. This will be assessed q 15 min x 2 hrs, then q 30 min x 2 hrs, then at hours 5, 6, 7, 8, 12, 16, 20, and 24 hours after administration of study medication. Standard questions will be asked to ascertain this endpoint, as listed in section 6.2.1 of the protocol: **"Taking into account all of the symptoms you experienced with this HAE attack, are you confident that it is starting to improve?"** To score the primary endpoint, subjects had to answer "yes" on 2 consecutive time points. Then the time of the initial positive response to the standard question was used to calculate time to initial relief of symptoms.*

Note that a "failure/poor" outcome of 24 hours was to have been imputed for any subjects who received either [masked] rescue study medication [Berinert or placebo] or analgesics or anti-emetics prior to the time of self-reported start of relief of HAE attack symptoms, because the administration of these medicines could affect the intensity of HAE attack symptoms and confound the primary efficacy (and several other efficacy) endpoint(s). In addition, the sponsor's representatives stated during a 12 November teleconference with FDA biostatistician Dr. Jean Wang, RPM Iliana Valencia, and myself that they also imputed a "poor/failure" value of 24 hours for subjects who received any of the following medications that were "Non-permitted" according to section 5.4 of the study protocol (final version 6.0 p 21 of 69):

- Any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis
- Open-label C1-INH
- FFP
- Attenuated androgens (for subjects not previously treated with androgens) or increased doses of androgens (for subjects already treated with androgens)
- Tranexamic acid (for subjects not previously treated with tranexamic acid) or increased doses of androgens (for subjects already treated with tranexamic acid)
- Aminocaproic acid (for subjects not previously treated with aminocaproic acid) or increased doses of androgens (for subjects already treated with aminocaproic acid)

It is noted, however, that the sponsor's representative's statement concerning imputation of a 24 hour value for the primary endpoint in relation to the administration of the above 6 "Non-permitted" medications appears to be at variance with Appendix Ivb to version 2.0 of the (final) statistical analysis plan dated 26 October, 2007 (approximately 1 month prior to the last subject completing the 7-9 day follow up of the study), in that the administration of androgens and "Transexamic [sic] acid, Aminocaproic acid," even if during the acute attack phase, did not affect the calculation of derived variable, TtRel⁺ (the primary endpoint, time to start of relief of attack symptoms, including imputed values of 24 hours for "poor/failure" outcomes). (This appendix was not present in the original statistical analysis plan). That the sponsor did not in fact impute 24 hours "poor/failure" outcomes for subjects that may have taken medications that have any of the pharmacological properties of C1-Esterase (other than C1-Inhibitor), attenuated androgens, tranexamic acid, or aminocaproic acid is suggested by various efficacy database field name definitions which include anti-emetics, analgesics, C1-INH, and FFP, but not the former medications (bullets 1, 4, 5, and 6).

SECONDARY ENDPOINTS: (strikeouts reflect protocol amendments)

- ~~Number of subjects receiving rescue medication~~
- Number of vomiting episodes within 4 hours after start of study treatment.
- Time between the start of study medication administration and complete resolution of all symptoms from evaluated (abdominal or facial) attack including pain as determined by the subject's assessment (TtrRes).
- Proportion of subjects with worsened intensity of clinical HAE symptoms at between 2 and 4 hours after start of study medication administration compared to baseline, for at least one of the HAE symptoms present at baseline.

- Area under the nausea intensity time curve between the start of treatment and 4 hours after start of study treatment.
- Number of bowel movements within 4 hours after start of study treatment.

ADDITIONAL VARIABLES

- ~~Number~~ *Proportion of subjects receiving rescue medication*
- Number of bowel movements within 4 hours after start of study treatment.
- Number of vomiting episodes within 4 hours after start of study treatment.
- Area under the nausea intensity time curve between the start of treatment and 4 hours after start of study treatment.
- Proportion of subjects with rescue study medication
- Plasma levels of C1-INH and C4 at baseline and 45 min (central lab).
- Time between the start of study medication administration and complete resolution of all symptoms from evaluated (abdominal or facial) attack including pain as determined by the subject's assessment (TtrRes). This was based on the subject's response to the question, "Have all symptoms of the HAE attack resolved completely"?
- Change and severity of symptoms (present at baseline) of the evaluated HAE symptoms (abdominal or facial) attack over time as stated by subject.

- Proportion of subjects with at least one new HAE symptom not present at baseline within 4 hours after start of study treatment. [This is required to be at least moderate intensity for 2 consecutive time points within 4 hours after start of study treatment.]
- Proportion of subjects with a time to onset of relief of symptoms of > 4.0 hours.
- For subjects with concomitant attacks concerning other body areas (skin, larynx, ~~face~~ in case subject shows up with an abdominal attack at the same time): Time to start of relief from symptoms of the concomitant attack as determined by the subject's assessment (**only if onset was at the same time as the abdominal or facial attack**).
- For subjects receiving rescue therapy, the time between start of rescue med administration the onset of resolution of HAE (abdominal or facial) attack as determined by subject's assessment.
- For subjects with facial edema: assessment of change in the severity of the edema based on photographic documentation.

PRE-PLANNED SAFETY POPULATIONS

Four different safety populations were planned, due to the use of rescue medication, one of which was further subdivided into 2 subpopulations:

- 4-hour safety population
- After-4-hour safety populations
 - Subjects receiving rescue study medication

- Subjects not receiving rescue study medication
- Overall-Beriner-safety-population
- Overall-safety-population (not analyzed by the sponsor)

STATISTICAL CONSIDERATIONS

For subjects receiving rescue medication, the time of onset of relief of abdominal symptoms was to be censored at the time of receipt of the rescue medication.

The primary efficacy analysis is a modified ITT analysis to have been performed on group 2 (high dose) and the placebo group using a 1-sided Wilcoxon test modified for censored data with an overall alpha of 0.025.

Kaplan-Meier curves were also planned and employed.

See section 7.2.1 of the protocol for the sponsor's definitions ITT [a misnomer as the sponsor defines it] and per-protocol analyses.

For the secondary efficacy variable consisting of the proportion of subjects with worsened intensity of clinical HAE symptoms at between 2 and 4 hours after start of study medication administration compared to baseline, for at least one of the HAE symptoms present at baseline, a 1-sided Fisher's exact test was to be used.

An exploratory per-protocol analysis has been added with amendment 3.

A Cox proportional hazard model with time dependent covariates (administration of rescue medication) was also performed.

A number of sensitivity analyses for the primary efficacy analysis and various subgroup analyses were planned as described on p 30 of 54 of the protocol (see CBER biostatistical review).

SAMPLE SIZE / STUDY POWER

Sample size calculations were modeled after the study of another product by ---b(4)----- which gave the difference in time to start of symptom relief between placebo and active groups as 0.75 hr for ITT, 0.84 hr for the first attack of each subject who actually had an attack, and 0.925 for the subject mean over several attacks. The

sponsor then modified this to a difference of 0.7 hr for the ITT, in view of the planned censoring. This provides a power of 68% for a 2 x 25-subject sample size comparison.

In an exploratory analysis TtRes will also be analyzed by a rank test stratified for type of attack (abdominal or facial).

For each of the secondary endpoints the conditional power at the time of the interim analysis was to have been calculated, for showing a one-sided trend with a $p < 0.1$ at the final analysis in favor of Berinert P (comparison of placebo group and Berinert P Group 2).

If case of missing data on worsening intensity of clinical HAE symptoms at 4 hours after start of study treatment, the last available data on change from baseline within 3 to 4 hours after start of study treatment will be carried forward to the 4 hour time point.

If it is not possible to identify time to start of relief from attack and to complete resolution of attack for a subject who did not receive rescue med, then the time to event will be 24 hours (poor/failure endpoint) for the time to start of relief, and will be censored at the latest time the subject confirmed not to have had resolution for the time to complete resolution.

REVIEWER'S ASSESSMENT OF PIVOTAL FACIAL AND GI EDEMA PROTOCOL

The plan for rescue medication, as originally conceived by the sponsor in the original IND submission, was judged to be a potentially fatal flaw to the study design, and was recommended to be changed. Even if the use of rescue medication is prohibited during the initial 4 hours, there were no controlled data with this particular product to allow us to judge whether efficacy, if seen, would be seen in the majority or all of such subjects by 4 hours. It was also noted that allowing the placebo group to be given the high dose of the active product at or after the 4 hour time point defeats one of the key purposes of having a placebo group, in terms of detecting/confirming safety problems. Because this product inhibits the fibrinolytic system and because 11 some-odd thromboses have been reported following administration of Berinert-P in postmarketing surveillance, the ability to compare the incidence of thrombotic events across treatment groups will be important. Giving the placebo group active product defeats this, and recognition of thrombotic events may easily be delayed hours or days. The sponsor states, however, that several European study sites would not participate in the trial if active product were not to be made available to

subjects as rescue medication. The sponsor has thus accepted CBER's alternate suggestion to modify the protocol to acknowledge and classify all Aes that occur following administration of rescue medication as potentially related to test product administration. This was later amended to assign a causality of at least possibly product related for all Aes that began within a pre-defined number of days following administration of the test article.

The use of time to initial pain relief is considered by CBER to be an unproven endpoint in this setting, though the sponsor's experienced expert consultant believes it is the best endpoint. This reviewer has articulated that a win on that endpoint should be accompanied by a statistically-significant (or very strong) trend in favor of the study drug in the time to complete resolution of symptoms for the study to be convincing. However, the sponsor stated that, due to the time typically needed for complete resolution of symptoms in relation to the time after which rescue medication is allowed (at or after 4 hours), it was pessimistic that a statistically significant difference in time to complete resolution of symptoms would be demonstrated. The sponsor was, however, optimistic that another secondary outcome efficacy variable will demonstrate a strong trend difference between the treatment groups: the proportion of subjects in each randomization group that receive rescue medication. The sponsor has calculated that it has > 80% power to detect a difference in this secondary endpoint with an alpha of 0.1. In view of the sponsor's confidence in this regard and the questions that persist regarding the clinical significance of a time to start of symptom relief and the choice of the latter endpoint as the primary efficacy outcome variable, this reviewer recommended that the statistical analytical plan be further modified to provide for a successful outcome of the study only if both of 2 co-primary endpoints meet the pre-specified acceptance criteria: The time to start of symptom relief by ITT must be better in the test group than in the control group (1-sided alpha 0.025) AND the proportion of subjects in each randomization group that receive rescue medication should show a difference in favor of the test group with a strong trend p value of ≤ 0.1 . This seemed a reasonable approach given the orphan nature of the study population and practical constraints on enrolling larger number of subjects to achieve a smaller alpha for both co-primary endpoints. CBER later accepted an alternate secondary endpoint consisting of the proportion of subjects whose baseline HAE symptoms worsened between 2 and 4 hours.

The IND record shows that whether a single phase III trial will suffice in combination with the overseas studies and postmarketing experience to support efficacy and safety of the product for this indication was deemed to require further discussion.

RESULTS of Study CE1145 3001

This phase 2/3 multinational placebo-controlled dose-ranging RCT was conducted between 14 Aug 2005 and 28 Dec 2007 (apparently not including the 12 week protocol-mandated viral safety blood sampling follow-up).

The study was conducted at 36 sites, of which 17 were in the U.S. Sites were located in 15 countries.

Number of Subjects: 126 (78 US, 48 foreign). Randomized: 125

ITT population: 124 (42 placebo, 39 Berinert P 10U/kg, 43 Berinert P 20U/kg)

Per protocol population: 120

History of Sample Size Adjustment and Addition of a 2nd Interim Analysis.

The originally planned sample size was 25 subjects per randomization group. The original protocol provided for a single interim analysis whose purpose was to permit sample size readjustment based on not only observed variance but also the observed magnitude of the treatment effect. Because there was no provision for early termination, there was no p value penalty for the first interim analysis. Based on the first interim analysis, at which point a total of 35 subjects had been enrolled in the high dose plus placebo groups, the DSMB recommended the sample size be increased from 25 to 100 per arm. Because the sponsor did not want to enlarge the study beyond 43 subjects per high and low dose arms and wanted to drop the low dose group, the sponsor, after negotiations with FDA, amended the protocol to perform a 2nd interim analysis at 25 subjects per high dose and placebo groups (actually conducted when 57 total subjects had been enrolled in high dose plus placebo arms), and to add criteria that the DSMB could use to recommend the low dose cease enrollment. The amendment also provided for a final analysis after 43 subjects would be enrolled in high dose and placebo groups, with adjustment for the final p value based on the interim look taken at the 2nd interim analysis, so that the overall alpha level would be preserved at 5%. The DSMB recommended stopping enrollment in the low dose group, but because each site's IRB had to approve a protocol amendment to cease enrollment into the low dose arm, the number of low dose patients who enrolled in the study (40) exceeded the number originally planned (25).

The final tally of subjects enrolled was:

20 U/kg randomization group: 43
10 U/kg randomization group: 40
Placebo group (saline): 42

Study dates: 14 Aug 2005 – 2 October 2007 (last patient completed day 7-9 visit)

Batched used in the trial: 14

Only a single abdominal or facial edema attack was evaluated per subject. Study day 1 was the day of administration of test article. Viral safety was assessed 12 weeks after treatment. Enrollment in Group 2, the 10 U/kg group was terminated for futility after the first interim analysis.

Exposure

| Treatment Group | First Infusion (Dose for acute treatment; study medication) | Possible second infusion after 4.0 hours (Rescue medication) | Mean Total dose actual Berinert including Rescue Medication (U/kg) |
|-----------------|---|--|--|
| Group 1 | 10 U/kg | 10 U/kg | 11.45 |
| Group 2 | 20 U/kg | Placebo | 13.33 |
| Group 3 | Placebo | 20 U/kg | 20.92 |

DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The Berinert P 20 U/kg group had a higher proportion of Type II HAE subjects (19% vs. 10% for placebo and 8% for Berinert P 10 U/kg group.

The randomization groups were comparable for sex, age, race, prevalence of androgen treatment, and distribution of attack locations. **Despite the adaptive randomization, the Berinert P 10 U/kg group had a smaller percentage of severe attacks compared to the other**

groups. The 10 U/kg group also had a smaller number of subjects with severe pain at baseline (6 vs. 10 in the Berinert 20 U/kg group and 15 in the placebo group).

| Treatment Group | Number/Percentage of Subjects having Severe HAE Attacks |
|-----------------------------|--|
| 1 Berinert P 10 U/kg | 7/18% |
| 2 Berinert P 20 U/kg | 16/37% |
| 3 Placebo | 16/38% |

Inspection of the sponsor's table 9 on p 70 of the CSR reveals that the Berinert 20 U/kg and placebo groups were reasonably well balanced in the proportion of subjects with moderate plus severe pain, nausea, vomiting, cramps, and diarrhea, as baseline HAE attack symptoms. In addition, the breakdown by attack location was well balanced across randomization groups:

| Treatment Group | Number/Percentage of Subjects having Abdominal HAE Attacks | Number/Percentage of Subjects having Facial HAE Attacks |
|-----------------------------|---|--|
| 1 Berinert P 10 U/kg | 34 (79.1%) | 9 (20.9%) |
| 2 Berinert P 20 U/kg | 31 (79.5%) | 8 (20.5%) |
| 3 Placebo | 33 (78.6%) | 8 (19%) |

OVERALL ATTACK TYPE DISTRIBUTION

Abdominal: 98 subjects (79%)

Facial: 25 subjects (20%)

Other: 1 subjects (1)

Use of Rescue Medication

The sponsor calculated the proportion of subjects in each randomization group who received blinded rescue study medication (C1-Inhibitor or placebo) after 4 hours as follows:

| Randomization Group | Proportion Receiving Blinded Rescue Medication | Percent Receiving Blinded Rescue Medication |
|----------------------------|---|--|
| Placebo | 23/42 | 54.8% |

| | | |
|------------------|-------|-------|
| 10 U Berinert/kg | 13/40 | 32.5% |
| 20 U Berinert/kg | 8/43 | 18.6% |

(It is not clear why the sponsor counts $n = 40$ for the denominator in the 10 U/kg Berinert group, given that there were 39 subjects in this group in the ITT population. Furthermore, the information in this table conflicts with the data presented in sponsor's Table 33 on p 105 of the CSR which states that the number of subjects whose used "any rescue medication" (which includes analgesics/antiemetics as well as blinded rescue medication) was 25 in the placebo group, 13 in the Berinert 10 U/kg group, and 10 in the Berinert 20 U/kg group. Table 11.38 (Attachment 4 of Amendment 16) gives a slightly different by treatment group in the use of rescue study medication in the ITT population:

| Randomization Group | Proportion Receiving Blinded Rescue Medication | Percent Receiving Blinded Rescue Medication |
|---------------------|--|---|
| Placebo | 24/42 | 57.1% |
| 10 U Berinert/kg | 13/39 | 33.3% |
| 20 U Berinert/kg | 8/43 | 18.6% |

Note that, by inspection of the Kaplan-Meier curve presented in table 11.2.1 (Attachment 2 in Amendment 16) there were at least 3 subjects in the placebo group who were censored due to receipt of rescue medication prior to 4 hours. Because this curve was based on the primary efficacy variable, "TtRel+," "rescue medication" in this case would refer to "any rescue medication" (open label C1-INH, masked CTM, analgesics, or anti-emetics given as concomitant medications).

Table 33 on p 105 of the CSR indicates the following breakdown for the use of analgesics/anti-emetics/C1-INH:

| Randomization Group | Proportion Receiving analgesics/anti-emetics/C1-INH |
|---------------------|---|
| Placebo | 2/42 |
| 10 U Berinert/kg | 1/39 |
| 20 U Berinert/kg | 1/42 |

It appears the sponsor's inclusion of "C1-INH" along with "analgesics/anti-emetics" in Table 33 from which the above table was constructed is either an error or refers to open label C1-Inhibitor but not to masked study rescue

CTM (Berinert or placebo rescue medication). It is not clear why the denominators do not quite match those of the ITT population. The denominator for the Berinert 20 U/kg group in Table 10.5, “Subject population for pre-planned subgroup analysis – ITT population,” is 43 subjects.

The following table is taken from Table Q1c in Amendment 17 and shows the proportion and percent of subjects by ITT randomization group who received “any rescue medication.” The sponsor probably made an error in defining this in the footnote to the table as “Rescue study medication, open label CTM, analgesics or anti-emetics until 4 hours after start of study medication prior to or after start of relief.” This differs from bullet 1 in the sponsor’s response to FDA requested analysis 1C of our fax of 21 August 2008 in that there is no “until 4 hours” time restriction.

| Randomization Group | Proportion Receiving “Any Rescue Medication” | Percent Receiving “Any Rescue Medication” |
|---------------------|--|---|
| Placebo | 25/42 | 59.5% |
| 10 U Berinert/kg | 13/39 | 33.3% |
| 20 U Berinert/kg | 10/43 | 23.3% |

Note that the breakdown by treatment group in the use of rescue study medication suggests a dose response effect and supports the notion of the efficacy of the product. Note also that the protocol specified that the use of rescue medication was intended to be for exceptional cases, yet its use was common, which complicates comparisons to placebo in the safety analysis. According to the sponsor, all subjects who had not reported initial relief of symptoms by 4 hours subsequently received study rescue medication.

The breakdown by treatment group in the use of “any rescue medication” (which includes open label C1-Inhibitor, open label CTM, analgesics, or anti-emetics), also supports the notion of efficacy of the 20 U/kg Berinert group compared with the placebo group (in the sponsor’s analysis). However, it was not possible to validate the sponsor’s breakdown of the administration of “any rescue medication” prior to initial relief of symptoms, or prior to complete relief of symptoms, because of the large amount of missing data entries for the start time and date of “discouraged” (anti-emetics and analgesics) and “Non-permitted) medications noted to have been administered in the concomitant medication database, ADCM. Although the sponsor representative stated in a teleconference held with Dr. Wang and Ms.

Valencia of this Office with the sponsor on 12 November 2008 that they imputed “poor/failure” outcomes of 24 hours for the primary endpoint analysis, time to initial relief of symptoms, for all subjects who received any of the 6 categories of medications “Non-permitted” by the protocol, Appendix IVb: “Impact of Concomitant Medications and Rescue medication on PP- and sub-population definition and on primary efficacy variable” (Original BLA submission Module 5, section 5.3.5.1.11.22) indicates that this was not the case, and that the key variable TTREL+ did not take into account androgens or transexamic [sic] (tranexamic) acid or aminocarproic [sic] (aminocaproic) acid. This appendix was appended to version 2.0 of the statistical analysis plan dated 26 October 2007, approximately 1 month before the last subject completed the day 7-9 follow up visit. A review of BIRAMS does not indicate that this final statistical analysis plan was ever submitted to the IND.

PROTOCOL DEVIATIONS/VIOLATIONS

Subject categories excluded from the PP analysis are listed in section 9.7.1.1.1 of the study report on pp 55-56 and included subjects taking > 90% of planned amount of study medication or who received study medication different from the randomization schedule or who received any non-permitted medications within 4 hours of the initial study medication infusion.

EFFICACY

The sponsor states that subjects administered Berinert P C1-INH 20 U/kg experienced significantly shorter time from administration of product to the time of onset of self-reported relief of symptoms (median 0.5 hours), compared to placebo (median 1.5 hours, $p = 0.0025$, primary efficacy endpoint). The review team has been unable to validate the sponsor's primary endpoint analysis because of missing and the possibility of inaccurate data for the start date and/or time of potentially confounding medications that, according to the protocol, if administered subsequent to enrollment and prior to the subject's self-reported time to initial relief of symptoms (TTREL) was to have resulted in imputation of a “poor/failure” value of 24 hours for time to initial relief of symptoms. In addition, the sponsor imputed a value of 24 hours for TTREL for subjects who received some, but not all medications “Non-permitted” by the protocol. The criteria the sponsor used in picking and choosing which of the 6 classes of “Non-permitted medications,” all of which may confound the interpretation of efficacy, is unclear. The sponsor is asked to redo the primary endpoint

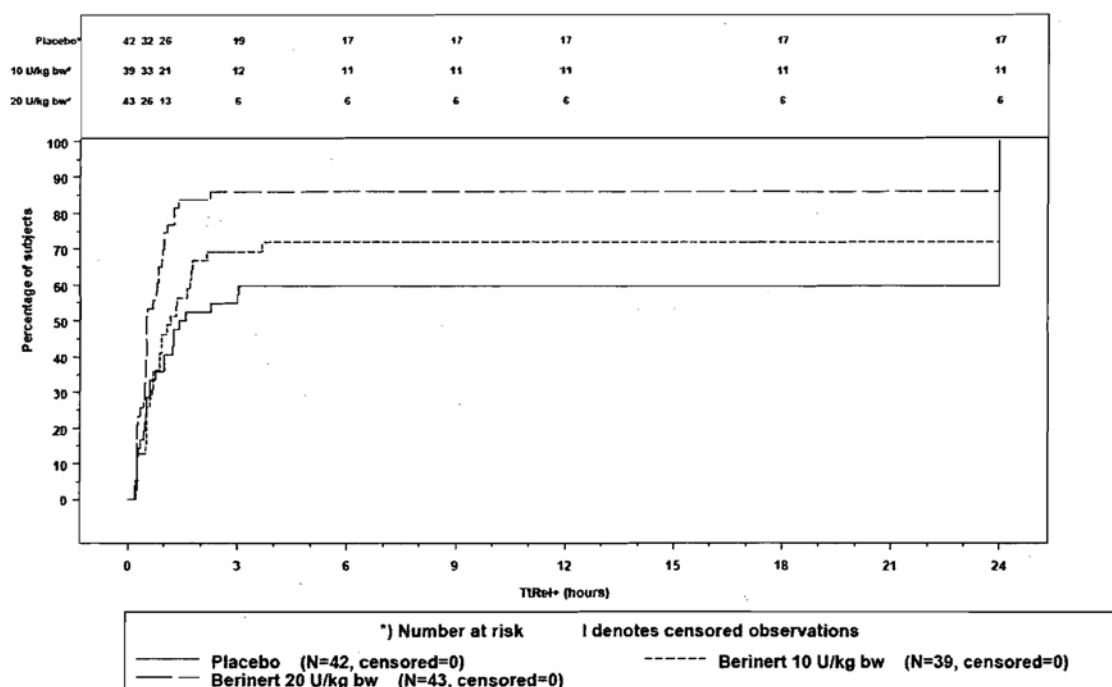
analyses on the ITT population imputing a value of 24 or 4 hours (depending on the analysis) for subjects who received any analgesics, anti-emetics, open-label or rescue study medication (Berinert or Placebo), or any of the 6 classes of “Non-permitted” medications between 5 hours prior to the time of administration of masked CTM and prior to TTREL, using data for the times of administration of these concomitant medications checked against hospital medication source records. This is needed because of the large amount of missing data for the start date/time of potentially confounding concomitant medications and conflicting data between the original CRF entries and investigators’ replies to sponsor-generated query forms concerning potentially confounding prior medications which were, according to the original CRF entries, being “continued” at the start of the trial.

In the 10 U/kg group the median time to initial relief of symptoms in the sponsor’s analysis was 1.17 hours. Because time to initial relief of symptoms was set to 24 hours for subjects who received any rescue medication prior to achieving a primary endpoint, the use of mean descriptive statistics can be misleading. The mean values for the primary endpoint were considerably higher than the medians, ranging from 3.89 hours for the high dose group to 7.47 hours for the low dose group to 10.26 hours for the placebo group, suggesting a skewed distribution with outliers in each treatment group. Again, the outliers were influenced by subjects receiving rescue medication having been imputed to have had an initial time to relief of symptoms of 24 hours, which skews the median data and the mean data, compared to if a shorter imputed time to initial relief of symptoms had been imputed for such subjects. Nevertheless, the 24 imputed value for time to initial relief of symptoms for subjects receiving rescue medication was regarded by FDA as conservative at the time the protocol was developed. Depending on the relative proportions of subjects receiving “any rescue medication” in each treatment group, the use of an imputed value of 24 hours for subjects receiving rescue medication may tend to magnify the between-randomization group differences in mean or median time to initial relief of symptoms, however. This seems to be the case with the actual observed trial data. **A better understanding of the between-treatment-group differences may be had by inspecting the Kaplan-Meier curves by treatment group for whether or not the primary endpoint has been met at each individual time point of assessment, censoring subject’s data at the time they are given any rescue medication.**

In order to score a primary endpoint, the subject was required to have answered in the affirmative on 2 consecutive occasions to the question, _____. The time of the initial positive response was used to calculate time from

administration of product to time to initial relief of HAE symptoms (abdominal or facial).

Figure 1 - Kaplan-Meier curves for time to onset of relief of HAE symptoms, as determined by subject's assessment (ITT population)



Time to onset of relief of abdominal or facial HAE symptoms by subject assessment¹ (ITT, from sponsor's table 13 on p 74 of study report)

| | Placebo N = 42 | Berinert 10 U/kg N = 39 | Berinert 20 U/kg N = 43 |
|----------------|-------------------|----------------------------|----------------------------|
| Mean (SD) | 10.3 (11.5) | 7.5 (10.5) | 3.9 (8.2) |
| Median (range) | 1.5 (0.20 – 24.0) | 1.2 (0.17 – 24.0) | 0.5 (0.17 – 24.9) |

¹These results are biased by the assignment of an imputed value of 24 hours for time to initial relief of symptoms for subjects who received rescue medication after 4 hours or who received either open label Berinert or analgesics/anti-emetics or FFP before 4 hours.

Dose finding – primary endpoint, ITT population

| Comparison of time to initial relief of HAE symptoms | P value |
|--|------------|
| Berinert 10 U/kg vs. Placebo | P = 0.273 |
| Berinert 20 U/kg vs. Placebo | P = 0.0025 |
| Berinert 20 U/kg vs. Berinert 10 U/kg | p = 0.0048 |

Breakdown in primary efficacy endpoint by HAE attack location

| Treatment Group | Median Time to Initial Relief of Symptoms – Abdominal Attacks (hrs) | Median Time to Initial Relief of Symptoms – Facial Attacks (hrs) |
|-----------------|---|--|
| Beriner 20 U/kg | 0.5 | 0.9 |
| Beriner 10 U/kg | 1.2 | 1.3 |
| Placebo | 1.3 | 24.0 |

Breakdown in primary efficacy endpoint by HAE attack Severity

| Treatment Group | Median Time to Initial Relief of Symptoms – Severe Attacks (hrs) | Median Time to Initial Relief of Symptoms – Moderate Attacks (hrs) |
|-----------------|--|--|
| Beriner 20 U/kg | 0.5 | 0.8 |
| Beriner 10 U/kg | | |
| Placebo | 13.5 | 1.3 |

Additional subgroup analyses of the primary endpoint by age and sex are discussed in Appendix 8.

During the IND stage, at my request the sponsor added individual symptom severity scores for each HAE attack symptom to the protocol. This was done with the express intent to compare reported changes in individual HAE attack symptom scores to the subjects' self-reported scores for the primary endpoint (time to initial relief of HAE attack symptoms). I carried out a manual analysis comparing the primary endpoint for each subject with a GI attack to the time when at least 1 GI attack symptom (cramps, diarrhea, nausea, pain, vomiting) had fallen by at least 1 point for 2 consecutive time points (analogous to the way the primary endpoint was scored, in terms of requiring a "yes" response to the primary endpoint question at 2 consecutive time points). In this analysis, I also required that no symptom increased in severity score (zero to 3 ordinal scale for none, mild, moderate, and severe). I also compiled the time to when at least 1 symptom had dropped by 2 or more points at 2 consecutive time assessment points, or when 2 or more symptoms had dropped by at least 1 point each, again providing no symptom had worsened in its score. The results of the analysis of time to when at

least 1 symptom dropped in severity by at least 1 category point revealed that there were inconsistencies between the results of looking at the set of individual GI symptom scores and the reported primary endpoint, time to initial relief of attack symptoms for a total of 27 of 67 subjects with GI attacks. In 20 cases, the sponsor-reported time to initial relief of symptoms was longer than the time to when at least 1 individual GI symptom improved by the minimum increment (1 point). In 7 cases, the sponsor-reported primary endpoint was shorter than the time to when at least 1 symptom improved by at least 1 point. These inconsistencies tend to undermine the sponsor's contention that the patient's self-reported time to initial relief of symptoms/primary endpoint in this trial represented the best efficacy measure for this type of product. In addition, it would be desirable in future studies of this or similar products to better understand the validation of efficacy endpoints as a function of specific attack location. A subject's ability to accurately identify the time to initial relief of facial or peripheral edema due to an HAE attack may potentially be quite different from his/her ability to accurately determine when nausea, cramps, or abdominal pain begins to subside.

In a post-hoc robustness log-rank test between Berinert 20 U/kg and placebo subjects performed by Dr. Wang of CBER DBE using the time to initial reduction in any individual GI symptom score by 1 severity category (none, mild, moderate, and severe) among GI attack subjects, the analysis demonstrated a significant difference in favor of the Berinert randomization group ($p = 0.02$)

Numerous "discrepancies" were also noted between the results of the DSMB's objective independent masked (blinded) analysis of serial facial photographs, generally taken at baseline then hourly, when compared to the subjects' primary endpoint times to initial relief of symptoms, among facial attack subjects. The frequency of disagreements seemed surprising; notwithstanding the possibility a subject might conceivably note an improvement in facial tightness prior to there being a discernable improvement in facial swelling. In fact, when these apparent disagreements were examined in conjunction with severity scores of individual facial symptoms, changes in facial tightness did not appear to explain the discrepancies. Of course facial photographs were taken less often than the primary endpoint question was asked. However this fact may explain only a few of the apparent disagreements between the subjective self-reported primary endpoint time to initial relief of symptoms and time to initial objective improvement in facial photographs as read by the DSMB.

See the biostatistical review memo for Kaplan Meier plots and log-rank test results for the time to initial improvement in facial photographs, as scored by the DSMB.

In a post-hoc landmark analysis, >75% of subjects in the 20 U/kg Berinert group reported initial relief of HAE symptoms by 1 hour, compared with ~40% of placebo subjects.

The study in its final protocol version had 2 secondary efficacy endpoints whose results were as follows:

- The proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of study drug, compared to baseline: Berinert P 20 U/kg 2/43 subjects (5%) vs. Placebo 13/42 subjects (31%) $p = 0.0014$. Berinert 10 U/kg 8/39 (20.5%).
- The number of vomiting episodes within 4 hours after the start of study treatment: Berinert P 20 U/kg 5/43 subjects with any vomiting (12%) vs. Placebo 11/42 subjects with any vomiting (26%) $p = 0.033$ for Wilcoxon test for number of vomiting episodes

The sponsor states that, although subgroup analyses suggested trends in greater efficacy for Berinert 20 U/kg among men, in facial vs. abdominal attacks, and in severe vs. moderate intensity attacks, the observed trends were not consistently maintained across the secondary variables.

The sponsor made note of between-subject variability in response, which they attributed to the underlying disease and differences in type of attack. “Facial attacks are generally characterized by large fluid shifts and take considerably longer to resolve.”

The study had several exploratory efficacy variables, among them:

- Time to complete resolution of symptoms of attack: Berinert P 20 U/kg median 4.9 hours vs. Placebo median 7.8 hours, $p = 0.024$.
- Proportion of subjects receiving rescue [study] medication: Berinert P 20 U/kg 8/43 (19%) vs. Placebo 24/42 (57%) [By contrast, in Table 10.5, it states that for Berinert P 20 U/kg 10/43 (23%), Berinert P 10 U/kg 13/39 (33%), and Placebo 25/42 (60%) were given “any rescue medication.”

- Proportion of subjects receiving any rescue medication including analgesics, anti-emetics, open-label Berinert: Berinert P 20 U/kg 10/43 (23%) vs. Placebo 25/42 (60%).

While results with the 20 U/kg dosing group were statistically superior to placebo, results with the 10U/kg dosing group showed a positive trend, but were not significantly different from placebo. (The lower, 10 U/kg arm was abandoned shortly prior to the end of the trial by the sponsor on recommendation of the DSMB (after CBER suggested the question be put to them), based on the fact the 1st interim analysis) was said to have shown a positive trend, but were not significantly different from placebo. The trend at first interim analysis for the 10 U/kg group was weaker than that of the 20 U/kg group, and this information was inappropriately conveyed by the DSMB to the sponsor during this otherwise blinded trial.

Time to Complete Resolution of HAE Symptoms Ignoring Potential Rescue Medication (ITT analysis)

| Statistic | Placebo | Berinert 10 U/kg | Berinert 20 U/kg |
|----------------|------------------|--------------------|--------------------|
| Mean (SD) | 125.1 (383) | 216.1 (494) | 81.8 (314) |
| Median (range) | 7.8 (0.3 – 1486) | 20.0 (0.47 – 1486) | 4.92 (0.47 – 1486) |

Note that all missing values were set to 1486 hours, indicating that there were missing values for time to complete resolution in all 3 randomization groups.

At 24 hours after study medication administration, > 75% subjects in the Berinert 20 U/kg group and > 60% of symptoms in the placebo group had complete resolution of HAE symptoms, according to the sponsor's analysis.

At CBER request, the sponsor also conducted analyses of the time from the onset of the attack to initial and complete resolution of the HAE attack. Although the randomization groups were somewhat unbalanced in the time from onset of the attack to onset of randomized treatment favoring the Berinert 20 U/kg group, these analyses, described in detail in Appendix 2, tended overall to support the efficacy of the product in the dose of 20 U/kg in comparison to placebo.

REVIEWER'S CONSLUSION REGARING EFFICACY IN IMPACT I STUDY

Taken in aggregate, the results of the various efficacy analyses support the notion of efficacy of Berinert 20U/kg for treatment of acute GI + facial attacks; however it is still necessary to validate the sponsor's primary endpoint analyses, which has not been possible due to missing data for the start date/time of potentially confounding concomitant medications.

Safety:

The original BLA safety analyses emphasize 3 safety populations:

| Safety Population Nomenclature | Number of Subjects across 3 arms |
|---|--|
| 4-hour safety | 126 ¹ (46 hi dose, 39 low dose, 41 placebo) |
| After 4-hour safety without rescue medication | 82 |
| After 4-hour safety with rescue medication | 44 |

Included in the 20 U/kg group of the sponsor's 4 hour safety population is one placebo subject, one 10 U/kg Berinert randomization group subject, and one non-randomized subject who received 20 U/kg of open label Berinert P during the first 4 hours. It appears that the sponsor has removed the placebo subject who received open label product from the placebo randomization group, yet did not remove the 10 U/kg randomization group subject who received open label Berinert P such that the total dose was > 15 U/kg from the Berinert P 10 U/kg group. This subject appears to be in both the 10 U/kg and the 20 U/kg groups in the sponsor's analysis.

The definition of the after 4-hour safety databases is not completely clear to this reviewer from the original IND and the sponsor was asked to clarify. Even the clarification stated that it included "all AEs," but it appears it included only AEs that began within 4 hours after randomized masked CTM was administered at time 0.

A footnote states that 1 subject each in the placebo and 10 U/kg groups, plus 1 not randomized subject received emergency study medication or, (in violation of the protocol), rescue Berinert P 20 U/kg within 4 hours after start of study medication.

AEs starting during initial 4 hours by "as treated" treatment group (not ITT)

| | Placebo (as treated) | High Dose Berinert P (as treated) |
|--|----------------------|-----------------------------------|
|--|----------------------|-----------------------------------|

| | | |
|-----------------------------|----------|---------|
| Total Subjects “as treated: | 41 | 46 |
| AE regardless of causality | 18 (44%) | 9 (20%) |
| At least possibly related | 8 (20%) | 5 (11%) |
| SAEs | 0 | 0 |

AEs starting after 4 hours by “as treated” treatment group (not ITT) subsets without rescue medication

| | | |
|---|----------------------|-----------------------------------|
| | Placebo (as treated) | High Dose Berinert P (as treated) |
| Total Subjects “as treated: | 18 | 38 |
| AE regardless of causality | 9 (50%) | 11 (29) |
| At least possibly related | 2 (11) | 4 (11%) |
| SAEs related to product (per investigator) | 0 | 0 |

One 20 U/kg Berinert P subject had an SAE that resulted in premature discontinuation from the study. However, for the 3 safety databases in the original BLA, the sponsor states that no deaths or Aes leading to a discontinuation of study medication occurred.

The most frequently reported Aes were nausea, diarrhea, pain, and muscle spasms.

Table 42 - Summary of AEs in >1 subject overall by preferred term and system organ class (4-hour safety population)

| System organ class Preferred term (MedDRA) | Placebo (N=41) | Berinert 10 U/kg bw (N=39) | Berinert 20 U/kg bw (N=46) |
|---|---------------------------|---|---|
| Number of subjects with at least 1 AE | 18 (43.9) | 10 (25.6) | 9 (19.6) |
| Gastrointestinal disorders | 13 (31.7) | 3 (7.7) | 5 (10.9) |
| Nausea | 5 (12.2) | 1 (2.6) | 3 (6.5) |
| Abdominal pain | 3 (7.3) | 1 (2.6) | 2 (4.3) |
| Diarrhea | 4 (9.8) | 1 (2.6) | 0 |
| Vomiting | 3 (7.3) | 1 (2.6) | 1 (2.2) |
| Lip swelling | 1 (2.4) | 1 (2.6) | 0 |
| General disorders and administration site conditions | 3 (7.3) | 5 (12.8) | 2 (4.3) |
| Pain | 1 (2.4) | 4 (10.3) | 1 (2.2) |
| Edema peripheral | 0 | 1 (2.6) | 1 (2.2) |
| Face edema | 1 (2.4) | 1 (2.6) | 0 |
| Musculoskeletal and connective tissue disorders | 4 (9.8) | 4 (10.3) | 1 (2.2) |
| Muscle spasms | 2 (4.9) | 4 (10.3) | 1 (2.2) |
| Nervous system disorders | 2 (4.9) | 2 (5.1) | 2 (4.3) |
| Dysgeusia | 0 | 1 (2.6) | 2 (4.3) ← |
| Headache | 2 (4.9) | 1 (2.6) | 0 |

Notes: The Berinert 10 U/kg bw group was ceased for fertility after the first interim analysis.

This table includes only SOC's with individual preferred terms that occurred in >1 subject overall.

N = total number of subjects

Source: Table 12.2 and Table 12.3

Table 46 - Possibly related AEs in >1 subject overall, by preferred term and system organ class (4-hour safety population)

| System organ class Preferred term (MedDRA) | Placebo (N=41) | Berinert 10 U/kg bw (N=39) | Berinert 20 U/kg bw (N=46) |
|---|---------------------------|---|---|
| Number of subjects with at least 1 possibly related AE | 8 (19.5) | 8 (20.5) | 5 (10.9) |
| Gastrointestinal disorders | 7 (17.1) | 3 (7.7) | 3 (6.5) |
| Nausea | 2 (4.9) | 1 (2.6) | 2 (4.3) |
| Abdominal pain | 1 (2.4) | 1 (2.6) | 1 (2.2) |
| Diarrhea | 3 (7.3) | 1 (2.6) | 0 |
| Vomiting | 1 (2.4) | 1 (2.6) | 0 |
| General disorders and administration site conditions | 1 (2.4) | 3 (7.7) | 2 (4.3) |
| Pain | 1 (2.4) | 3 (7.7) | 1 (2.2) |
| Edema peripheral | 0 | 1 (2.6) | 1 (2.2) |
| Musculoskeletal and connective tissue disorders | 3 (7.3) | 4 (10.3) | 1 (2.2) |
| Muscle spasms | 1 (2.4) | 4 (10.3) | 1 (2.2) |
| Nervous system disorders | 2 (4.9) | 2 (5.1) | 2 (4.3) |
| Dysgeusia | 0 | 1 (2.6) | 2 (4.3) |
| Headache | 2 (4.9) | 1 (2.6) | 0 |

Note: The Berinert 10 U/kg bw was ceased for futility after the first interim analysis.

N = total number of subjects

Source: Table 12.4

The sponsor postulates that the efficacy of the product was responsible for the smaller incidence of AEs among Berinert arm subjects compared to placebo subjects. This explanation seems plausible, given that several of the most frequently reported AEs comprise abdominal HAE symptoms which may have progressed more in the placebo arm than in treated arms.

Note that the only AE occurring among at least 2 subjects whose frequency was greater in the 20 U/kg arm than in the placebo arm in the 4 hour safety population was dysgeusia (disordered taste sensation).

AEs by Severity and by Treatment Arm in 4 hour Safety Population

| | Placebo (as treated) | High Dose Berinert P |
|---|----------------------|----------------------|
| Total Subjects | 41 | 46 |
| Severe AEs regardless of causality | 11 (27%) | 1 (2%) |
| Severe AEs at least possibly related | 4 (10%) | 1 (2%) |
| | | |

For complete listings of all AEs by frequency and by organ system for the 4 hour safety population and for the “Overall Berinert P safety population (n = 108), please see Appendix 3 of this review. The latter safety population appears to include all AEs reported in the low and high dose Berinert P arms plus AEs that began following infusion of Berinert as rescue medication in the Placebo arm. Note that 23 subjects in the placebo arm received rescue medication and one received open label Berinert. Also note that one non-randomized “subject” was administered 20 U/kg open label Berinert and included in the sponsor’s safety analyses. As noted previously, the sponsor appears to have double counted a Berinert 10 U/kg randomization group subject in who received open label Berinert.

AEs by Severity and Seriousness and by Treatment Arm in After 4 hour Safety Population Without Rescue Medication

| | Placebo (as treated) | High Dose Berinert P |
|--------------------------------------|----------------------|----------------------|
| Total Subjects | 18 | 38 |
| Severe AEs regardless of causality | 1 (6%) | 3 (8%) |
| Severe AEs at least possibly related | 0 (0%) | 0 (0%) |
| SAEs | | 2 (5%) |

In all original BLA safety populations, all severe AEs and SAEs resolved without sequelae.

The sponsor concluded there were no clinically significant differences between treatment groups in changes from baseline in vital signs or physical exams.

Viral Safety

No seroconversions were observed for HIV-1, HIV-2, HAV, HBV, HCV, or Parvovirus B19.

REVIEW OF SELECTED CASE REPORT FORMS (CRFs)

General comment on CRFs:

The response to the primary endpoint question was not always consistent with the changes in intensity scores of individual symptoms over time. See the following example for subject -b(6)----:

| Symptom | baseline | 90 min | 120 min |
|----------------|-----------------|---------------|----------------|
| pain | moderate | mild | mild |
| nausea | moderate | none | none |
| vomiting | none | none | none |
| cramps | moderate | mild | mild |
| diarrhea | severe | none | none |

I would have expected this subject to have reported initial improvement in the HAE attack, taking all symptoms into account, by the 90 and 120 minute time points (if not before), yet the subject answered “No” to the primary endpoint question, “” Taking into account all of the symptoms you experienced with this HAE attack, are you confident that it is starting to improve?”

Furthermore, the CRF entries for changes in symptoms from baseline were not always consistent with my comparison of numerical severity score entries for individual HAE attack symptoms. For subject -b(6)-, the large number of crossed out CRF entries for “Change of symptom” on the ASSESSMENT OF HAE ATTACK pages strongly suggests that when the CRF was originally filled out, the CRF completer believed he/she was supposed to record the change from the previous assessment time point, rather than the change from baseline as instructed (in unbolded italicized smaller font) on the CRF.

A summary of pertinent CRF entries for selected subjects is presented in Appendix Item 2

REVIEW OF 19 JUNE 2008 SAFETY UPDATE BLA AMENDMENT RECEIVED 20 JUNE 2008

The cut-off date for this submission was 07 May 2008

SAFETY UPDATE FOR CE11145_3001 IMPACT I STUDY

The last subject completed the study 28 Dec 2007.

The study was unblinded when all data up to the day 7 to 9 visit were declared clean for all subjects.

Unblinding occurred before 3 month viral follow-up testing data were available for all subjects.

As a result, the following sections of the final study report as presented in the original BLA have been affected:

Sections 2, 10.1, 12.3.1.2, 12.5.3, 12.6, 13, 14, and 16.

Following an internal audit, the following additional sections were updated “to implement some other minor formal updates.”

Section 5.3

Section 10.2.2

Section 11.2.2

Section 11.4.4.1

Section 12.2.1

Section 12.2.3

Section 12.2.3.1

Section 12.5.1

The above sections relate to safety, vital signs, protocol deviations, informed consent, plasma levels of C1-INH and C4, but do not relate to efficacy.

SUMMARY OF SAFETY UPDATE FOR IMPACT I (PIVOTAL) STUDY

The sponsor concluded that the updates to the AE data did not have an impact on the safety profile described in the original study report.

One additional SAE (laryngospasm) was reported in subject --b(6)-- that occurred ~ 6 weeks after administration of Berinert 20 U/kg and was considered not related.

The additional 12 week follow-up data revealed no seroconversions for HIV-1 or 2, HAV, HBV, HCV, or Parvovirus B19.

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.

Protocol Deviations

The most frequent protocol deviation was failure to ask questions regarding improvement of symptoms in the specified time window, which occurred for 54 of 127 subjects (44%). This had the potential to affect the primary endpoint. Note that the protocol allowed the primary endpoint question not to be asked if the patient was asleep. Nevertheless, one would anticipate that most subjects with an HAE attack sufficient to prompt hospitalization would be awake from their ongoing symptoms

Concomitant Medications

The most frequent or notable concomitant medications taken for HAE were sex hormones and “modulators of the genital system” (Danazol) (3/42 placebo subjects, 6/39 Berinert 10 U/kg subjects, and 4/43 (9.3%) of Berinert 20 U/kg subjects), the anabolic agents xandrolone or stanozolol ((2/42 placebo subjects, 2/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects), analgesics (4/42 placebo subjects, 4/39 Berinert 10 U/kg subjects, and 2/43 (4.7%) of Berinert 20 U/kg subjects), fentanyl (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 0/43 of Berinert 20 U/kg subjects) ibuprofen or ketorolac tromethamine (1/42 placebo subjects, 2/39 Berinert 10 U/kg subjects, and 1/43 (%) of Berinert 20 U/kg subjects), vicoprofen (1/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 0/43 of Berinert 20 U/kg subjects), ASA (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 0 /43 of Berinert 20 U/kg subjects), prednisone (0/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects), promethazine (2/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 2/43 (4.7%) of Berinert 20 U/kg subjects), hydroxyzine (1/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects) plasma protein fraction (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects), anti-emetics/anti-nauseants (1/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects). Note that the sponsor separated into several different pharmacologic classes drugs which mechanistically should be combined into the same or related class.

Levels of C1-INH and C4

“Minor” updates were provided to the data for C1-esterase inhibitor (C1-INH) activity, C1 antigen concentration, and C4 plasma levels during the

first 4 hours after study medication administration. Tables 5 and 6 in the safety update (SU) update these data.

Mean C1-INH Plasma Levels (%) in Relation to Time Zero Masked Study Medication Administration

| STATISTIC | PLACEBO N = 37-42 | BERINERT 10 U/KG M = 34-39 | BERINERT 20 U/KG N = 36- 43 |
|---------------------------------------|----------------------|----------------------------------|-----------------------------------|
| BASELINE | 16.6 | 10.9 | 14.2 |
| CHANGE FROM BASELINE TO 1 HR | -3.7 +/- SD 7.6 | 24.5 | 43.2 +/- SD 22.2 |
| CHANGE FROM BASELINE TO 4 HR | -2.8 +/- SD 7.1 | 22.2 | 37.8 +/- SD 18.0 |

C1 Antigen Plasma Levels (mg/dL) in Relation to Time Zero Masked Study Medication Administration

| STATISTIC | PLACEBO N = 35-42 | BERINERT 10 U/KG N = 33-39 | BERINERT 20 U/KG N = 36-43 |
|---------------------------------------|----------------------|----------------------------------|----------------------------------|
| BASELINE | 10.0 | 8.8 | 12.4 |
| CHANGE FROM BASELINE TO 1 HR | -1.5 | 5.2 | 13.1 +/- SD 8.2 |
| CHANGE FROM BASELINE TO 4 HR | -2.1 +/- SD 5.0 | 5.1 | 10.1 +/- SD 5.7 |

C4 Plasma Levels (mg/dL) in Relation to Time Zero Masked Study Medication Administration

| STATISTIC | PLACEBO N = 35-42 | BERINERT 10 U/KG N = 38-39 | BERINERT 20 U/KG N = 35-43 |
|----------------|----------------------|----------------------------------|----------------------------------|
| BASELINE | 8.2 | 7.3 | 8.0 |
| CHANGE FROM | -2.7 +/- SD 11.3 | -0.1 +/- SD 5.0 | -0.8 +/- SD 7.5 |

| | | | |
|---------------------|--|--|--|
| BASELINE TO 4 HR | | | |
|---------------------|--|--|--|

ADVERSE EVENTS – Safety Update

One Berinert 20 U/kg subject experienced laryngospasm > 4 hr after administration of Berinert, judged by the investigator to be unrelated to the test product.

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).

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.

Note: Change to the protocol by current and prior amendments are indicated by strikeout and underlining.

EXTENSION PROTOCOL No./TITLE: CE1145_3003 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 ~~and/or CE1145_3002~~ [acute laryngeal edema study].

Note: Change to the protocol by current and prior amendments are indicated by strikeout and underlining.

PHASE OF INVESTIGATION: II/III

OBJECTIVES

PRIMARY

- To document the use of pasteurized C1-INH concentrate (Berinert P) in the treatment of all kinds of HAE attacks.

SECONDARY

- To document the safety and efficacy of Berinert P in subjects with HAE.

DESIGN SUMMARY FOR EXTENSION STUDY

The ongoing open label extension of 2 a phase III trials is multinational, prospective, involving ~~25 centers~~ up to 30 centers enrolling subjects with C1-INH deficiency who qualified for ~~either of the pivotal trials 3001 or 3002~~ by having an acute moderate to severe abdominal or facial ~~or acute laryngeal~~ attack. Subjects screened for study 3001 but who develop acute laryngeal attacks prior to enrollment in 3001 may now be enrolled in this extension protocol. The duration of the extension protocol is ~~24~~ 36 months from when the last subject enrolls or until product licensure, whichever comes first. Time to the start of abdominal pain relief, a subjective endpoint, is the proposed primary endpoint to be analyzed by a Wilcoxon rank test. Viral safety f/u at 3 months is planned. A DSMB will monitor study safety. The primary analysis will be the ITT population. Subjects will be counted as non-responders regarding the analysis of the primary endpoint, if they have received rescue medication.

PROPOSED NUMBER OF SUBJECTS: up to 60

COORDINATING INVESTIGATOR:

Timothy Craig, D.O.
Allergy & Respiratory Research
Penn State U.
Hershey, PA

INCLUSION CRITERIA

- Prior ~~inclusion~~ eligibility for study CE1145_3001 ~~and/or CE1145_3002~~.
- Any HAE attacks.
- Treatment with study medication in study _3001 ~~and/or CE1145_3002~~ more than 24 hours ago except in the case of laryngeal edema.
- Written informed consent.

EXCLUSION CRITERIA

- Life expectancy < 6 months
- Incurable malignancies with metastases
- 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)
- End-stage liver disease (i.e., Child-Pugh score B or C)
- HIV positive
- 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 concentrate within the previous 24 hours.
- Treatment with ACE inhibitors within the previous 4 weeks.
- Treatment with FFP 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 EtOH abuse).

Selected details of study methods:

Enrollment ends 2 months after termination of pivotal study CE1145_3001.

Withdrawn subjects will not be replaced.

All HAE attacks [involving any body site] occurring after completion of the 24 hour evaluation in the pivotal study are eligible for treatment with a single dose of 20 U/kg of Berinert C1-INH under this protocol.

Onset of time to initial and complete relief of HAE attack symptoms will be performed as in pivotal study CE1145_3001. Diaries will be used to record time to total resolution of attack if subject is discharged before attack has completely resolved.

The investigator will assess the time to initial relief of symptoms every 15 min x 2 hrs, then q 30 min 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 will prompt

the question: **“Have all symptoms of the HAE attack resolved completely?”**

The subject will be asked to specify more precisely the exact time within the past time interval.

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

The study is uncontrolled and open label.

Subjects on prophylactic treatment with androgens, tranexamic acid, or aminocaproic acid may be included but the dosage must be kept constant after the onset of an attack until it resolves completely.

Forbidden Concomitant Medications:

- Any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis.
- Additional open label C1-INH in excess of 20 U/kg.
- FFP
- Attenuated androgens if not already on androgens
- Tranexamic acid if not previously treated with same.
- Aminocaproic acid if not previously treated with same.

CAUSALITY ASSESSMENT FOR AEs:

- Not related: “The event can be readily explained by factors not involving the IMP and a temporal relationship with the investigational medicinal product does not exist.”
- Possibly related: “A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.”
- Probably related: “The temporal relationship between administration of the IMP is compelling, and the event cannot be explained by the subject’s medical condition or other therapies.”

- Related: “The event follows a reasonable temporal sequence from administration of the IMP, follows a known response pattern to the IMP, is confirmed by improvement upon stopping the IMP (dechallenge) and reappears upon repeated exposure (rechallenge).”

ANALYTICAL PLAN

The study had a stand-alone statistical analysis plan (SAP). Version 2.0 of the SAP is dated 26 October 2007, only ~ 1 month before the last subject completed the study on 28 December 2007. The original SAP was dated 5 March 2006. (The study began 14 Aug 2005). Note that OBRR/DH/CRB, since at least January, 2007, has had a policy that the final SAP should be submitted to FDA at the time the final protocol is submitted. The sponsor did not comply with this Clinical Review Branch expectation. Note that the final version 6.0 of the protocol was dated 23 May 2007.

PRIMARY ENDPOINT

- *Time between start of study medication administration and onset of relief of symptoms from an HAE attack determined by subject's assessment. This will be assessed q 15 min x 2 hrs, then q 30 min x 2 hrs, then at hours 5, 6, 7, 8, 12, 16, 20, and 24 hours after administration of study medication.*

SECONDARY ENDPOINT:

- Time between start of study medication administration and complete resolution of all symptoms of the HAE attack.

ITT and Per-Protocol analyses will be conducted. *The following subjects will be excluded from the ITT population to generate the per-protocol population:*

- Attacks for which study medication administration was not fully compliant, i.e., ~~<90%~~ <75% of planned.
- Attacks due to acquired angioedema diagnosed after enrollment, or due to any non-HAE cause for abdominal pain.
- Attacks if the subject had been treated with C1-INH within the previous 24 hours

- Attacks if the subject had been treated with FFP or native plasma within the previous 7 days.
- Missing entries for both efficacy criteria, TtRel and TtRes.
- Violating the major inclusion criterion, “prior inclusion/eligibility for Study CE1145_3001
- Evidence of narcotic seeking behavior and/or drug addiction (including alcohol abuse).
- Fulfilling the exclusion criterion, “narcotic pain medication and/or anti-emetics between start of attack and administration of study medication.

The primary endpoint will be analyzed on both per attack and per subject bases, the latter by averaging the outcomes for each attack of a given subject. The distribution of both of these outcomes will be described by descriptive statistics as well as Kaplan-Meier graphs and 95% CIs for the mean and median.

Subgroup analyses will include:

- By country
- By sex
- By HAE types I or II
- By age ranges of 3 to < 12, 12 to < 17, 17 to < 65, and ≥ 65 years.
- By race
- By whether concomitant Danazol, Stanazolol, or Oxandrolone is being taken
- By HAE attack type

SAFETY VARIABLES:

- AEs
- Vital signs
- Virus safety by antibodies (HIV1&2, HAV, HBV (including HbsAg), HCV, parvovirus B19 (including IgM)) and by -b(4)- (HIV-1, HAV, HBV, HCV, Parvovirus B19) for 1st attack only at baseline and week 12 (day 7-9 for Parvovirus B19 -b(4)-)

OVERVIEW OF EFFICACY ACROSS TRIALS

Only the pivotal phase II/III was randomized and masked. Thus, combining efficacy data from the pivotal trial and its open-label extension study is not appropriate. The sponsor notes, however, that very similar mean times to initial relief of symptoms were seen in the pivotal trial and in the extension trial's first interim analysis submitted with the original BLA.

INTERIM RESULTS OF ONGOING OPEN-LABEL EXTENSION STUDY CE145-3003

The sponsor states that the interim results of the primary endpoint of this open-label uncontrolled U.S./Canadian extension study (identical endpoint to that of the feeder phase 3 protocol _3001) were identical to that of the blinded phase II-III Impact I “feeder” trial. Subjects could be enrolled in this trial as early as the 24 hour assessment after administration of test article under the feeder protocol (or earlier if laryngeal edema) and treated under the extension protocol for HAE attacks at any location that were deemed to require treatment with product. AEs were collected for up to 7-9 days after product administration and viral data were collected 3 months after product was given. Sixty subjects were planned to be enrolled in the extension study. The interim analysis of the extension trial (cutoff date 29 June 2007) comprises 355 HAE attacks in 39 subjects (26 females and 13 males) at “any body location.” The sponsor claims there were “identical” results for time to onset of relief of symptoms for abdominal and peripheral edema attacks and “similar” results for facial and laryngeal attacks.

The primary endpoint of the extension study was the same as for IMPACT I, TTRELP. Median TTRELP was 0.48 hours. By 1 hour, $\geq 90\%$ of subjects reported start of symptom relief from their HAE attack. This percentage is higher than in IMPACT I, possibly due to the bias of an uncontrolled study where everyone knows they are getting an active product.

Median times to onset of relief of symptoms was similar for the subgroup of subjects taking androgens to those not taking androgens.

The secondary endpoint was time to complete relief of symptoms.

Median time to complete relief of symptoms after Berinert 20 U/kg in the extension study interim analysis was 13.8 hours. At 24 hours > 75% of subjects had complete resolution of symptoms. The median time to complete resolution of laryngeal attacks (n = 6 subjects) was 2.41 hours, compared to a median of 29.5 hours for facial attacks (n = 5 subjects). Abdominal attacks (n = 33 subjects) resolved in a median of 10.62 hours and peripheral attacks (n = 19 subjects) resolved in a median of 22.5 hours.

SAFETY IN THE EXTENSION STUDY, IMPACT II

Blood for viral safety assessment was drawn only for the first attack.

See the section below for safety analysis on the safety of the update to the extension study (cutoff 07 May 2008) for more complete safety data on the Extension study than was included in the original BLA submission.

No deaths were reported.

Of 39 subjects enrolled as of June 2007, 16 (41%) reported AEs. Six reported 8 severe AEs. All AEs resolved without sequelae. Four subjects had AEs considered at least possibly related to study medication. Two subjects had SAEs considered unrelated to CTM by the investigator. **One subject discontinued from the study due to an infusion related reaction (no details given).** The most frequent AEs were headache in 4 subjects, HAE [attack\exacerbation] in 3 subjects and nasopharyngitis in 3 subjects.

SUMMARY OF SAFETY UPDATE FOR IMPACT II OPEN LABEL EXTENSION STUDY CE1145_3003

The June 19 2008 Safety Update (SU) in (vols 3-4 of the SU) consists a synopsis and tables, graphs and listings. The cutoff date for the addendum was 07 May 2008. The extension study is ongoing and involves 13 U.S. and 1 Canadian Center. As of the May cutoff, 56 subjects had enrolled in the SU. These 56 subjects had experienced a total of 559 that were available in the database. The percent of subjects reporting abdominal attacks was 85% (68% of treated attacks); those reporting peripheral attacks numbered 28 (50% of subjects), and comprised 24% of attacks. Facial attacks were observed in 11 subjects (20%) and totaled 20 attacks, of which 2 were mild, 12 were moderate, and 6 were severe. (Extension study subjects were ~ 2/3 female and ~ 1/3 male with a mean age of 32 years. Of the 56 subjects, AEs

were reported for 21 (38%) of subjects. Seven subjects (12.5%) reported severe AEs. All subjects with AEs in the database recovered without sequelae except one who had a URI. The most frequently reported AEs were headache and HAE [attack], the latter reported for 4 subjects. Other AEs occurring in 5% or more of subjects were abdominal pain in 3 subjects (5%) and nasopharyngitis in 3 subjects (5.4%). Seven subjects reported AEs considered at least possibly related to the test article (abdominal discomfort, headache, infusion related reaction, dry mouth, influenza like illness, rash, and dizziness. Between the time of the first interim analysis cutoff on 29 June 2007 and 07 May 2008 there were no deaths and no new SAEs or AEs leading to discontinuation of CTM or from the study reported. Including the entire study period through 07 May a total of 2 (3/6%) of subjects experienced SAEs (HAE, staphylococcal infection, neither considered related to CTM). Both SAEs resolved without sequelae. **One subject had an “infusion related reaction” that lead to discontinuation of study medication (Berinert).**

AE Breakdown by Age in the Extension Study Update

Subjects with AEs by Age Category

| Age Range | No. Subjects with AEs | AEs/No. Treated Attacks |
|-------------------|------------------------------|--------------------------------|
| 3-11 years | 0/1 | 0/26 |
| 12-16 | 2/6 | 2/26 |
| >16-64 | 19/49 | 41/507 |

Review of individual AE preferred terms in Table 12.12.4.1 by subject age did not reveal any age-specific patterns. Notable AEs were rash in 2 subjects, dizziness in 1 subject, joint swelling in 1 subject, pyrexia in 1 subject, and “Infusion related reaction” in 1 subject.

The sponsor could not discern any consistent or clinically relevant changes in review of vital sign changes.

For 4 attacks, physical exam at 24 hours showed worsening of an HAE attack despite Berinert 20 U/kg administration.

No update in viral safety data was available in this update report to the extension study.

**REVIEW OF BLA AMENDMENT 10 (0.10) DATED 17 JUNE 2008
CONCERNING IMMUNOGENICITY TESTING**

This amendment was submitted in partial response to requests discussed with the sponsor during teleconferences and conveyed by fax on 15 April 29908. The fax questions read as follows:

12. Please submit the results of anti-C1-INH antibody testing for the Canadian site subjects for the pivotal trial.

14. Please submit an amendment to your ongoing U.S. extension study to provide for measurement of anti-C1-INH antibodies. If positive samples are obtained, it will be necessary to determine whether the antibodies are inhibitory. If positive samples are obtained, testing of baseline stored specimens may be explored to determine whether the test results were “treatment emergent.”

The sponsor first replied to the above requests in its amendment dated 15 May 2008. Included in this 17 June submission is anti-C1-INH testing data on subjects participating in the open label extension study to the pivotal trial, namely extension study CE1145_3003.

Because this antibody testing was not pre-planned, samples for the testing were taken from residual volumes of samples intended for vital safety testing at baseline (before administration of study product in the open-label extension) and at 12 weeks after the baseline visit of the extension study. Samples were first tested with a direct binding --b(4)-- screening test, followed by confirmatory testing of positive samples using an anti-C1-INH isotyping assay. If a positive sample was confirmed, it was then tested in an inhibitor assay. The validation data for these assays was submitted in a separate amendment dated 15 May 2008 and is being reviewed by the Product/CMC review team.

The screening assay lower limit of normal was set using data from “at least 100 samples from healthy normal subjects” to allow a false positive probability of about 5% in order to minimize false negatives.

The anti-C1-INH isotyping assays were similar to the screening assays, but used 3 different -----b(4)----- antibodies for detection of isotypes ---b(4)-----. Titers were determined against calibration with positive, isotype specific material.

The anti-C1-INH antibody inhibitor assay was similar to the ----b(4)-----
----- assay. -----b(4)-----
-----, and the residual C1-INH
activity measured using the ----b(4)---- C1-INH --b(4)-- Assay
(----b(4)-----) and compared to normal control samples.
[Reviewer Comment: It is not clear whether the inhibitor assay included a
known positive control.]

Information is presented for 57 subjects, which includes 53 subjects from 13
US centers and 3 subjects who did not participate in randomized study
CE11145_3001. The source of the additional subjects is unclear. Of the 57
subjects, the 3 that were not part of the pivotal study plus 8 who received
only placebo in the pivotal study had not received Berinert prior to inclusion
in the open label extension study. Thus, 46 subjects were tested for
antibodies among those who had previously received Berinert.

Of the 57 subjects, no samples were available for 4 (subjects ----b(6)-----
-----). In the remainder, the extension study baseline sample is
missing and in 4 others the week 12 of the extension study samples were
missing.

In all, 16 of 46 subjects tested above the cut-off in the screening anti-C1-
INH antibody assay, either at baseline or week 12 of the extension study. Of
these, 13 tested above normal both at baseline and week 12. Of these 13
who tested positive twice during the extension study, 6 tested below the
cutoff at screening [of the pivotal trial] and 7 were above the cutoff at
screening. One additional subject was positive at screening, positive at
baseline of the extension study, and missing a sample at week 12.

Of the 8 subjects positive at screening, 4 had reportedly no prior exposure to
C1-INH or FFP, according to personal communications from the
investigators. The sponsor notes that in the paper by Varga et al. [1996],
anti-C1-INH antibodies were also detected in subjects who had not reported
prior exposure to C1-INH containing products.

Of the 16 subjects tested above the cut-off, 12 were treated with Berinert
only and 2 were treated with placebo.

The titers of anti-C1-INH antibodies were “very low” in all samples tested
above cut-off. Antibodies from subject samples ranged in titer up to a
dilution of 1:50, whereas positive control serum titers were 1:31250 or
1:156250.

Of the 16 subjects who were above the cut-point on the screening assay, 12 were confirmed by isotyping and 4 were not confirmed. Of these, 5 were IgA only, 2 were IgG only, 4 were both IgG and IgA, and one tested positive for IgG, IgA, and IgM.

No inhibitory C1-INH antibodies were detected among the 12 subjects whose positive screening antibody test was confirmed by isotyping. In 5 cases the inhibitor assay was conducted on different material (either plasma or serum) than had been used for screening and confirmatory assays due to sample volume constraints.

Reviewer's conclusion regarding antibody testing:

The fact that subjects with treatment-emergent positive C1-INH antibody results did not have detectable inhibitors in the sponsor's assay is reassuring, provided the CMC review team is satisfied with the inhibitor assay validation data. However, the appreciable incidence of 6 of 46 subjects having treatment-emergent confirmed positive anti-C1-INH antibody testing raises the question of whether testing of larger numbers of subjects exposed to the product would yield some with positive inhibitors. This may be addressed in a post marketing commitment, which will also permit assessment of antibody and inhibitor status in more subjects with a larger number of repeated exposures to the product.

**REVIEW OF BLA AMENDMENT 0.19 DATED 24 SEPTEMBER 2008
REGARDING SAFETY UPDATE**

This amendment responded to CBER's fax information request sent 03 September 2008 for electronic databases to support the safety updates to the pivotal and open extension studies that were submitted as a BLA amendment on 19 June 2008, among other requests.

CBER's 03 September 2008 fax information request numbered items with sponsor's response in italics and reviewer comments in bold:

1. Please submit updated electronic databases to support the updated subject data listings contained in your "Clinical Study Update" submitted June 19, 2008.

Sponsor Response:

Provided.

Reviewer Comment:

Noted.

2. Using the above updated databases, please provide AEs by preferred term, grouped by body system, including subject ID numbers, for (a) all AEs reported for the group randomized to placebo, censoring data for each subject who received blinded rescue or open-label medication starting at the time rescue/open-label Berinert was administered and (b) subjects randomized to the 20 U/kg group plus data for subjects randomized to the placebo who received (20 U/kg) rescue medication starting for these placebo subjects when they received blinded rescue medication. These analyses should include (a) all AEs, (b) AEs judged by the investigator or sponsor to be at least possibly related to administration of rescue study medication), and (3) all AEs minus those identified in the protocol as being compatible with symptoms of a GI HAE attack.

For each analysis of AEs, please provide both summary statistics as well as a table listing the output of each analysis in terms of lists by treatment/treatment group of each AE (preferred and verbatim term) with time of onset and severity of each AE. Please include-b(4)- code for all AE analyses.

Sponsor Response:

The sponsor provided the requested analyses, but for analysis (b), included AEs judged by the investigator to be at least possibly related to administration of rescue study medication (or beginning within 72 hours of the start of any administration of rescue study medication). CSLB notes that the analyses regarding (a) all AEs and (b) all AEs minus those identified in the protocol as being compatible with symptoms of a GI HAE attack had previously been requested by CBER in the fax of 15 April 2008. The sponsor refers to their 16 July 2008 response that contained Tables Q4C1.1, Q4C1.2 and listings Q4C1 and Q4C3.

CSLB detected a programming error related to the generation of Tables Q4C in the 16 July 2008 response. This submission contains a corrected update of the Q4C analysis. The other analyses presented in the 16 July 2008 response were not affected by the programming error.

The sponsor believes the requested analysis combining data for subjects in the placebo group after they received Berinert 20 U/kg together with the Berinert 20 U/kg randomized subjects' data is biased favoring the placebo group as predominantly placebo subjects did not improve within 4 hours and received rescue Berinert and the sponsor presumes that such subjects had more AEs [related to worsening HAE symptoms].

Reviewer Comment:

Regarding the sponsor's interpretation of analysis (b), because data for placebo subjects are censored at the time of receipt of rescue study medication, the sponsor's interpretation of what was requested in this analysis should be acceptable. Regarding the concept of bias favoring the placebo group in this analysis, the sponsor was offered the option to correct the denominator by using subject-hours of exposure, but declined to do so. In addition, any bias resulting from inclusion of placebo subjects who receive Berinert rescue along with subjects randomized to Berinert would be expected to pertain only to HAE symptoms. Thus the requested analysis that removes HAE GI symptoms specified in the protocol is of particular interest. Ignoring AEs that occur in placebo subjects who receive Berinert 20 U/kg as masked rescue medication would ignore potentially important safety data regarding Berinert.

The following table corresponds to analysis of all AEs from item 2 above:

Table Sep3Q2 1.1: Summary of adverse events- Subject population:RP2*, Adverse event population: AEs censPlac Rescue**

| | | Berinert 20 U/kg and Open-label) | | | |
|--------------------------|--------------|---|---------------|-----------|---------------|
| Statistic | | Placebo | | | |
| Subjects treated | N (%) | 42 | (100) | 67 | (100) |
| Subjects with AEs | N (%) | 28 | (66.7) | 37 | (55.2) |

Subjects with at least possibly related AEs

| | | | | | |
|--|-----------|---------------|--|-----------|---------------|
| | 10 | (23.8) | | 18 | (26.9) |
|--|-----------|---------------|--|-----------|---------------|

| | | | | |
|----------------------------------|----------|--|----------|---------------|
| Subjects with serious AEs | 0 | | 3 | (4.5) |
|----------------------------------|----------|--|----------|---------------|

Subjects with at least possibly related serious AEs

| | | | |
|--|----------|--|----------|
| | 0 | | 0 |
|--|----------|--|----------|

| | | | |
|-------------------------------------|----------|--|----------|
| Subjects who died due to AEs | 0 | | 0 |
|-------------------------------------|----------|--|----------|

Subjects who died due to at least possibly related AEs

| | | | |
|--|----------|--|----------|
| | 0 | | 0 |
|--|----------|--|----------|

Study drug permanently discontinued due to AEs

| | | | |
|--|----------|--|----------|
| | 0 | | 0 |
|--|----------|--|----------|

| | | | |
|---|--|--|----------|
| Subjects with AEs that were serious/led to permanent discontinuation | | | 0 |
|---|--|--|----------|

| | |
|----------|---------------|
| 3 | (4.5) |
|----------|---------------|

The following table corresponds to analysis (3) of item 2 above, in that protocol-specified HAE GI symptoms have been removed:

Table Sep3Q2 2.1: Summary of adverse events- Subject population:RP2*, Adverse event population: AEs in AEs minus HAE 2 and in AEs censPlac Rescue**
(AEs minus HAE 2: AEs not compatible with HAE symptom according to protocol, i.e. excluding nausea, vomiting, abd. pain and cramps, and diarrhea.)

| Statistic | | Placebo | | Berinert 20 U/kg (Randomized, Rescue and Open-label) | |
|--|--|-----------|---------------|--|---------------|
| Subjects treated N (%) | | 42 | (100) | 67 | (100) |
| Subjects with AEs N (%) | | 18 | (42.9) | 29 | (43.3) |
| Subjects with at least possibly related AEs | | 6 | (14.3) | 12 | (17.9) |
| Subjects with serious AEs | | 0 | | 2 | (3.0) |
| Subjects with at least possibly related serious AEs | | 0 | | 0 | |

Subjects who died due to AEs 0

0

Subjects who died due to at least possibly related AEs N (%)

0

0

Study drug permanently discontinued due to AEs

0

0

Subjects with AEs that were serious\led to permanent discontinuation

0

2

(3.0)

***: Risk population 2 (RP2): All subjects of the ITT20UvsPlac population. Subjects randomized to placebo who also receive the Berinert 20 U/kg rescue study medication and subjects randomized to placebo who received the open label Berinert emergency medication are counted both in the placebo group and in the Berinert 20 U/kg group.**

****: AE72horRel censPlac Rescue**

- AE assessed to be possibly related to the test article (i.e. Berinert or placebo) according to the investigator or sponsor.

- AE beginning during or within 72h or the start of any infusion of Berinert rescue study medication.

24SEP2008 / 12:20 / aaesumq2.-b(4)-

3. Please submit comprehensive cumulative line listings and narrative summaries for all 57 suspected adverse reactions (ADRs) for the period 1985 through December 2007. The 2 PSURs and their updates you submitted collectively cover only the period 1999 onward and did not include cumulative line listings of ADRs. Please be sure to include all available details concerning the 4 cases of suspected viral transmission by your product.

Sponsor Response:

The sponsor states that “expected” AEs are those contained in the Company Core Safety Information (CCSI), which is based on the ADRs included in the product information of countries in which Berinert is licensed. Those not included in the package insert [CCSI] are described as “unexpected.”

Overall, 37 of 57 reported ADRs are “expected” using the above definition. These include 5 vases of suspected virus transmission, 14

cases of thrombosis, 7 cases of allergic/anaphylactic reactions, 2 cases of chills and fever, and 9 cases of lack of effect

Attachment 6 of the amendment contains details of the reported ADRs.

Table 1 shows 2 cases of anaphylactic reaction/anaphylactic shock and one of BP decrease to 90/40 in which the causality was assessed by the sponsor as possible.

Table 5 on p 6 of Attachment 6 of the amendment lists 5 cases of suspected virus transmission by the product resulting from spontaneous postmarketing reporting. In each case, the sponsor has rated causality as unlikely. The cases are summarized below.

| <i>Company Case ID</i> | <i>ADR</i> | <i>Serious ?</i> | <i>Comment</i> |
|------------------------|--------------------------------|------------------|--|
| <i>-----b(6)-----</i> | <i>Hepatitis C</i> | <i>Yes</i> | <i>Lot produced from HCV genome negative tested source plasma</i> |
| <i>-----b(6)-----</i> | <i>Hepatitis B</i> | <i>Yes</i> | <i>Product last given 2 years prior to diagnosis. Pt reported "very close contact" with a high-risk population during a trip through Africa which had occurred 2-3 months before the diagnosis of hepatitis B.</i> |
| <i>-----b(6)-----</i> | <i>CMV Infection</i> | <i>Yes</i> | <i>This infection occurred in a 2 month old baby. The reported incubation period was only 1 day. The reporting MD assessed a "connatal" infection as the most probable cause.</i> |
| <i>-----b(6)-----</i> | <i>"HGV" (-b(4)-) Positive</i> | <i>No</i> | <i>This case of hepatitis G seroconversion occurred in an unsponsored study. No other reports of suspected virus transmission regarding the involved lots were obtained, but testing was not described. The sponsor states that the manufacturing process has demonstrated high virus inactivation/ elimination capacity for BVD, a model for hepatitis G.</i> |
| <i>-----b(6)-----</i> | <i>Hepatitis B</i> | <i>No</i> | <i>This female was diagnosed with hepatitis B in 2003 several months after receiving Berinert. Despite queries, no further information was provided. The</i> |

| | | | |
|--|--|--|---|
| | | | <i>implicated lot was manufactured from HBV-b(4)- negative source plasma.</i> |
|--|--|--|---|

Reviewer Comment:

Regarding hepatitis C, no information is provided regarding risk factors or whether the sponsor attempted to obtain additional data.

Regarding hepatitis B, the first case is apparently confounded by a risk factor in the subject and had a 2 year delay in the diagnosis from last exposure, but there is nothing to rule out the 2nd case except for the negative result with testing source plasma by -b(4)-. It would be helpful if the sponsor distinguished between acute and chronic hepatitis B.

Regarding CMV, the stated delay from last product administration to onset of CMV infection is 1 day, which is too short.

Regarding the hepatitis G case that occurred in a study not sponsored by CSLB, the sponsor notes no other viral seroconversions from the implicated lots, but gives no information as to whether the other subjects in the study were tested for hepatitis G.

The above suspected seroconversion information should also be reviewed by DBE and by the DH product review team/Committee Chair in view of what is known concerning the manufacturing process and inspectional findings.

Review of “Guide to datasets and programs for 12-week follow-up analysis of study 3001.”

The original BLA submission’s database was closed on 14 November 2007. The database was reopened to enter 12-week follow-up safety data, including viral safety follow-up data. New AE data were added as well as final assessment data for subjects who had not finished the study “until” [read as of] 12 November 2007. In addition, C1-INH antibody results were entered. Corrected and new data made a new follow-up analysis necessary. Programs and datasets are in folder STATISTICAL\3001-_FOLLOWUP in the CD-ROM submitted with this amendment 19. Some of the original analysis programs had to be updated due to the new data status “and because of changed layout definitions.” Relevant program changes compared to the initial analysis can be found in the program header of each updated program.

Note that the safety update submission of 19 June 2008 stated that no changes to efficacy data or results occurred as a result of the safety update. However, that submission also stated that there were changes to the concomitant medications data, which may affect the calculation of TTREL_P (time to initial relief of symptoms including imputation of 24 hours for subjects who received any rescue medication, including various concomitant medications, prior to TTREL (time to initial relief of symptoms)).

Amendment 19 states that the primary endpoint TTREL₊ was derived from the datasets ADHEATK (evaluation of HAE attack) and ADHAEBAS (HAE baseline information) combined with ADEX (treatment with study drug) and ADCM (concomitant attacks).

Programs and data sets for the safety update are in the CD-ROM

The sponsor notes that subject --b(6)-- was treated and not randomized at his initial HAE episode after screening. Later, he was “correctly included in the study as subject --b(6)--. Since there was no safety data available before randomization for subject --b(6)-- the subject was not included in the analysis. To simplify data handling it was decided to remove all data ...under subject ...--b(6)-- from the analysis datasets. The data is provided in separate datasets.”

SAFETY REVIEW OF SELECTED FOREIGN STUDIES

Study 7B—201CH-B

Study Title: C1-Inactivator Substitution during Extracorporeal Circulation

Study Site:

Study dates: 1988 – 1989

Objective: To investigate the effects of C1-Inactivator (BI 3.012) in addition to standard treatment, on the course of postoperative performance of patients having undergone extracorporeal circulation.

Design: Placebo (1% albumin) controlled, double-masked RCT in 30 subjects (15 per group) undergoing extracorporeal circulation during cardiac surgery. The dose of the product was 3500U (38 to 58 U/kg).

Complications were reported for 16/30 subjects (9 placebo and 7 test). One subject treated with C1-Inhibitor died of staphylococcal septicemia 11 days following hospital discharge on day 19. **This subject also had an acute MI on the day of surgery** and shock 6 days after surgery. These AEs were not ascribed to the test treatment by the investigator. No other thrombotic events were reported in the trial.

Reviewer Comment: The MI on the day of surgery may have been causally related to C1-Inhibitor administration.

Study 7B-201CH-C

Study Title: C1-Inactivator Substitution during Extracorporeal Circulation

Study Site: Prof. M. Lamy, Hopital de Vaviere, Liege, France

Study dates: Feb 1987 – May 1987

Objective: To investigate the effects of C1-Inactivator (BI 3.012) in addition to standard treatment, on the course of postoperative performance of patients having undergone extracorporeal circulation.

Design: Placebo (1% albumin) controlled DB, RCT enrolling males undergoing extracorporeal circulation to receive elective CABG. Subjects had no impairment of cardiac [!] or respiratory or renal function, no diabetes, severe hypertension, endocrine disorders, or severe anemia. Efficacy variables were surrogate endpoints reflecting CV performance and lab parameters reflecting activation of the “cascade systems.” Berinert 2500 U or placebo were given prior to heparin 2500 U. Only descriptive statistics were planned.

Results:

Fifteen subjects were enrolled and analyzed per group. Age range 37 – 77. No statistical differences were observed in CO, PAMP, PCWP, AaDO₂, PaO₂. C3d rose in both treatment groups indicating activation of the complement system despite administration of C1-Inhibitor.

AEs between days 0 and 2 included:

| AE | No. in Placebo Group | No. in C1-Inhibitor |
|----|----------------------|---------------------|
|----|----------------------|---------------------|

| | | Group |
|-------------------------|---|-------|
| Bleeding | 3 | 5 |
| Vasoconstriction | 0 | 1 |
| Cardiac insufficiency | 2 | 4 |
| Pulmonary insufficiency | 1 | 0 |
| Renal insufficiency | 0 | 1 |
| Confusion | 0 | 1 |
| Totals | 6 | 11 |

The table above indicates that nearly twice as many potentially serious/significant AEs were reported in the C1-INH treatment group.

SAFETY REVIEW OF UNCONTROLLED OLDER STUDIES IN HAE

STUDY 7d-201CI-OB

No AEs were reported in this small uncontrolled study of 9 subjects. The sponsor did not conclude there were any safety signals from lab data.

STUDY ce1145_6001

This was an uncontrolled retrospective analysis of pregnant women with HAE who received CE1145 (C1-Inhibitor). The sponsor concluded it was safe and well tolerated with no harmful effects on the embryos.

OVERVIEW OF SAFETY ACROSS STUDIES

See also Review of Safety Update. Note that in the statistical table of contents for extension study CE1145_3001 the sponsor states “Datasets and programs of the extension study have not been submitted. To facilitate the review of the safety summary data sets an annotated CRF is included together with a placeholder define.pdf document.”

The sponsor performed several pooled analyses of studies HAE studies CE1145_3001 and CE1145_3003, attempting to take into account the different study designs. The main focus was in the “Union 4 hour safety populations,” since under the first study, rescue study medication could be

administered after 4 hours at investigator/subject discretion. This population uses the first 4 hours observation period following CTM in both studies. In the first interim analysis of open extension study_3003, 39 subjects received a median of 5 administrations each of 20 U/kg Berinert for a median of 5 attacks per subject (range 1-59 attacks). In the “Union 4 hour safety populations,” 17 of 75 (22.78%) of Berinert 20 U/kg subjects reported AEs compared to 18 of 41 (43.9%) of placebo subjects (Module 2 p 32 of tab 2.7.4). The number of subjects with AEs considered at least possibly related to study medication was 8/75 (10.7%) Berinert subjects and 8 of 41 placebo subjects (19.5%). The differences between treatment groups appear to be due to a greater incidence of worsening HAE symptoms being counted as AEs in the placebo group. In the Berinert 10 U/kg group the number of subjects with AEs was 10/39 (25.6%) and the number reporting AEs considered at least possibly related to study medication was 8/39 (20.5%). No deaths occurred within 4 hours of study medication. One subject in the 4 hour safety population had an SAE not considered by the investigator to be related to CTM administration. One subject had a possibly related AE leading to discontinuation of study medication in the extension study (the sponsor refers to BLA see section 2.7.4.2.1.4 for details, but this section does not list the nature of the AE). Of 399 attacks treated with Berinert 20 U/kg, 19 (4.8%) were associated with AEs and in the case of 9 attacks, one or more AEs were considered at least possibly related.

Summary Statements regarding BLA:

The sponsor’s analysis concludes that the product met the primary endpoint and both secondary efficacy endpoints and that a dose-response was seen, although the efficacy results for the 10 U/kg group were not significant compared to placebo. This reviewer and the CBER biostatistician reviewer of this file been unable to validate the sponsor’s primary endpoint analysis, despite several information requests and teleconferences with the sponsor, due to missing data for the start date and time of administration for a large number of concomitant medications whose use, if prior to the self-reported time to start of relief of HAE attack symptoms, should have, according to the protocol, should have resulted in the sponsor imputing a “poor/failure” value of 24 hours for the primary endpoint for such subjects. However, given that the study was a masked (double-blind) randomized study, an intent-to-treat analysis ignoring the effect of concomitant medications should have validity, provided there was not an unusual imbalance between treatment groups in the use of such medications during the acute attack phase. Unfortunately, the data provided thus far by the sponsor have not permitted the review team to validate the sponsor’s analysis of the breakdown by randomization group

in potentially confounding “discouraged” and “Non-permitted” medications administered during the first 4 hours after masked CTM was administered. This again is because of the large number of missing start date/start time entries for analgesics, anti-emetics, and “Non-permitted” medications. I recommend the sponsor be asked to provide the administration times of such medications from the hospital medication records, and to provide copies of such records from the time window 5 hours prior to until 24 hours following the time zero time of administration of randomized masked CTM.

As the sponsor points out, reported treatment group mean times to the start of relief of symptoms are biased because, for subjects who received rescue medication, one cannot know what their time to initial relief of symptoms would have been without rescue medication. For this reason, and because the protocol allowed rescue study medication only after 4 hours, FDA asked the sponsor to provide an analysis of the time to initial relief of symptoms that imputed a value of 4 hours for subjects who received any rescue medication. As it turns out, the choice of either 4 or 24 hours for imputing time to initial relief of symptoms for subjects who received either open label or blinded test product, whether as rescue medication after 4 hours or in violation of the protocol before 4 hours, and for subjects receiving blinded rescue medication as placebo, and for subjects receiving analgesics or anti-emetics, has no effect on the log-rank p values, for between-group differences in the primary endpoint, or on treatment group median time to initial relief of symptoms. In addition, p values in both the sponsor’s supplementary analyses requested by FDA by fax on 21 Aug 2008 and in the FDA biostatistician’s analyses, censoring reported times to initial relief of symptoms when either masked rescue study medication or “any rescue medication” was administered produces very similar results to imputing a value of 4 hours for such “poor/failure” subjects.

The use of blinded rescue medication was frequent and imbalanced between treatment groups. Its use in active and placebo arms was much more frequent than expected from the language of the protocol. The protocol stated that the use of rescue medication should be in exceptional cases. As a result, the CBER biostatistician and I concluded that a better way of displaying the primary endpoint data is a Kaplan-Meier analysis limited to the first 4 hours. In the sponsor’s analyses, there were 4 subjects who received open label product prior or “any rescue medication” prior to the 4 hour point, however, FDA has thus far not been able to verify this as noted above. It should be noted that the 4 hour time point on the CBER-generated Kaplan-Meier curve based on TTREL gives values for the proportion of responders different from the landmark analysis of the proportion of subjects who have initial relief of symptoms by 4 hours, because the latter analysis

excludes the few subjects who received open label product before 4 hours. **The ~ 2.5 -fold excess in the proportion of subjects who received blinded rescue therapy in the high dose group in comparison to the placebo randomization group supports the notion that 20 U/kg of the test product is effective.** It should be noted, however, that scrutiny of the raw data for the primary endpoint reveals that some subjects randomized to high dose active product were non-responders. In a robustness analysis performed by myself and the CBER biostatistician, comparison of individual subjects' data for individual GI symptom scores over time to those subjects' reported primary endpoint result of time to initial relief of symptoms revealed that in ~ half of subjects with GI attacks the timing of individual GI symptom score changes did **not** support the subjectively reported time to initial relief of symptoms used by the sponsor for the primary endpoint. This highlights a limitation to the accuracy and validity of the primary endpoint. Nevertheless, the validity of the sponsor's analysis of the primary endpoint was supported by the finding of a statistically significant difference between the Berinert 20 U/kg randomization group and the placebo group in time to initial decrease by at least 1 category in self-reported individual GI symptom severity favoring the investigational product with a p value of 0.02. Like in the protocol-specified analysis of the primary endpoint, a decrease by at least 1 category (none, mild, moderate, severe) at 2 consecutive time points was required to score and endpoint in this robustness analysis, and no symptom was permitted to have increased from baseline at either of those time points. It is perhaps not surprising that there should be some differences between time to initial self-reported relief of GI attack HAE symptoms and time to initial decrease by 1 severity category of individual GI symptoms if subjects can discern finer gradations of symptom severity than those of the 4 point scale used in this study.

A similar robustness analysis was performed on subjects with facial HAE attacks. Here again, there were many differences between individual subject's time to initial relief of facial HAE attack symptoms, as scored by the subject's response to the primary endpoint question, and the time to the first reduction in facial symptom severity by at least 1 severity grade. Note that there were for the most part only 2 facial symptoms reported (facial swelling and facial tightness), unlike the case for GI attacks which had a larger variety of symptoms (cramps, abdominal pain, nausea, vomiting). The robustness analysis in the much smaller group of subjects with adequate individual facial HAE attack symptom data was not significant ($p > .6$) but the Kaplan-Meier curve of this robustness analysis showed a trend in favor of the test article as did the primary endpoint analysis of facial HAE attack subjects ($p = 0.16$ in the FDA analysis). The weak statistical evidence in favor of efficacy of Berinert for facial attacks may relate to a difference in

the validity of subjective patient assessments of changes in facial symptoms such as edema and tightness compared to their validity in the assessment of GI attack symptoms. It seems intuitively likely that subjects' ability to discern gradations of change in facial edema may be quite different than their ability to discern perhaps finer gradations in severity of nausea, abdominal pain, or cramps. It is also noteworthy that the median times to initial and times to complete relief of symptoms were much longer for facial attacks than for abdominal attacks.

Because sponsor's primary endpoint analysis was positive for the overall study population as well as the GI attack subgroup, and given that the study was not powered to necessarily obtain statistically significant results for each HAE attack location type studied (GI, facial), and because there was a trend, albeit statistically weak, in efficacy for the facial attack subgroup, it seems reasonable to grant an indication corresponding to the entire study population of GI plus facial HAE attacks. However, due to the weak statistical evidence of efficacy for the facial attack subgroup, I recommend the sponsor be requested to commit to a PMC to conduct an additional study in facial attacks which will also afford an opportunity to obtain additional longer-term safety and particular immunogenicity data.

It is noted that the median time to onset to relief of symptoms in the placebo group was 1.5 hours. This was shorter than the 4 hours by which it was hypothesized that subjects in the product-treated group would start to have improvement in symptoms. For complete resolution of the HAE attack in the placebo group the median time was 7.8 hours, which was 2.9 hours longer than the median time to complete relief of symptoms in the Berinert P 20 U/kg group.

The safety data presented in the BLA and safety update do not raise any special or unusual concerns in the setting of HAE other than the need to obtain additional immunogenicity data in a larger number of subjects who have received multiple exposures to the product, presenting a stronger immunologic challenge. More data are needed to attempt to correlate treatment-emergent positive anti-C1-Inhibitor antibodies with adverse events. It is reassuring that all such antibodies reported in the BLA were non-neutralizing. **While high doses of CSLB's C1-Inhibitor have been associated with 14 thrombotic events, mostly among pediatric patients undergoing cardiac surgery, the minimum dose associated with thrombosis is unknown.**

The use of rescue medication after 4 hours at the discretion of the subject and his/her investigator complicated the safety analyses. Because the incidence of treatment-emergent AEs was actually greater in the placebo group than in the Berinert groups in the 4 hour safety population, the sponsor was asked to perform additional safety analyses that excluded pre-defined HAE symptoms listed in the protocol. I have recommended this analysis be presented in the package insert, together with an additional analysis that combines AEs that were reported either after initial randomized Berinert or after masked Berinert given as rescue medication, compared to subjects who received placebo only.

LIST OF APPENDICIES

Appendix 1 - Summary of CRF Entries - Subject --b(6)--- – p 101

Appendix 2 - Complete listings of all AEs by frequency and by organ system for the 4 hour safety population and for the “Overall Berinert P safety population (n = 108) – p 104

Appendix 3 - Review of Sponsor Responses to 20 December 2007 CBER IND Information Request Letter – p 110

Appendix 4 - REVIEW OF SPONSOR AMENDMENT 6 DATED 15 May 2008 (RESPONSES TO CBER INFORMATION REQUEST FAXES TO SPONSOR DATED 16, 21, AND 23 APRIL 2008 – p 123

Appendix 5 - REVIEW OF SPONSOR AMENDMENT 7 DATED 30 May 2008 (RESPONSES TO CBER INFORMATION REQUEST FAXES TO SPONSOR DATED 21 April, 16 MAY, AND 28 MAY 2008) p 132

Appendix 6 - REVIEW OF SPONSOR AMENDMENT 13 DATED 16 July 2008 (RESPONSES TO CBER INFORMATION REQUEST FAX TO SPONSOR DATED 15 April 2008) – p 134

Appendix 7 - REVIEW OF SPONSOR AMENDMENT 16 AND 17 DATED 3 September 2008 AND 12 September 2008 (RESPONSES TO CBER INFORMATION REQUEST FAX TO SPONSOR DATED 21 AUGUST 2008) - p 140

Appendix 8 – Subgroup Analyses of Impact I study by Age and Sex – p 147

APPENDICES**Appendix 1 - Summary of Pertinent CRF Entries - Subject --b(6)--****Module 5.3.7 – Pivotal study CE145_3001**

Screening: 17 Mar 2006

Consented: 30 Mar 2006

Randomization Requested: 30 Mar 2006

Diagnosis Date: Aug 1989

Date CRF pages initialed/completed: 26 April 2006

HAE Type 1

PMHx: -b(4)-

Baseline PE: Clinically significantly abnormal abdomen

No radiology, DRE, or recto-vaginal exam performed to rule out other causes abdominal pain.

Baseline CBC, serum amylase, troponin, UA NOT DONE

Baseline C1-IH and C4 obtained at 12:15 on 30 Mar 2006.

Baseline BP 132/86, HR 71, RR24 (abnormal), afebrile

Abdominal attack began 30 Mar 2006 at 00:01, intensity: moderate by both subject and investigator; became moderate or severe at 11:20 that day. Symptoms all moderate except severe diarrhea. Pt had moderate pain, nausea, cramps, but no vomiting; also mild swelling right elbow but normal skin exam. Abdominal distension noted.

Study drug administered 166 mL for 82.9 kg at 12:38 to 12:47.

At 13:05, subject was not confident the HAE attack was starting to improve. Pain and cramps had increased to 3 from 2 at baseline, but nausea, and diarrhea decreased to 1 [in just 18 min from the end of the infusion!]. Vomiting, mild, (1 episode) had worsened from none.

At 13:20, symptoms were not starting to improve. **All symptoms were now rated severe, including vomiting, even though the subject had no episodes of vomiting since the last assessment! One BM since last assessment.**

At 13:30, vomiting and diarrhea had decreased to mild, yet the CRF states that vomiting had worsened (vomiting unchanged was crossed out). Diarrhea was improved (unchanged was crossed out). Curiously, right index finger and upper lip swelling were recorded and crossed out under “Other symptoms.”

At 13:55, symptoms were not starting to improve. Pain had decreased from 3 to 2, but pain “better” was crossed out and replaced with no change. Nausea was still severe, but a “3” corresponding to

“worse” was recoded, after having crossed out “unchanged.” Cramps were now “1” (mild) instead of “2” (moderate), but “1” (better” was crossed out and replaced with “2” no change. Diarrhea was still a “1”, but this was changed from “2” (no change” to “1” (better), compared to baseline. The subject had 1 vomiting and 1 BM since last assessment.

At 1:57 a C1-INH sample was obtained.

At 13:50 BP had decreased to 110/72 and HR had decreased to 56, RR now 20.

At 14:12, symptoms were not starting to improve (primary endpoint question. Pain, nausea, vomiting, and cramps were all rated mild, and all had improved from baseline, except vomiting, which had worsened (unchanged crossed out). No BM and no vomiting since last assessment.

At 14:30, the response to the primary endpoint question concerning whether “Taking into account all of the symptoms you have experienced with this HAE attack, are you confident that it is starting to improve?” was still “No.” Yet now the only remaining symptoms were mild pain and mild cramps. All symptoms except vomiting were described as improved from baseline, even cramps and diarrhea were originally recorded as “2” (no change) from baseline. Vomiting was changed from improved to unchanged from baseline. No BM and no vomiting since last assessment.

1 hr 45 min assessment: not done. “Subject asleep” NOT marked.

15:00 assessment: Same as 14:30 assessment. Primary endpoint question response still “No.” No BM or vomiting since last assessment.

15:35 Primary endpoint Q response: “No.” Abdominal attack symptom intensities: Pain 2 (unchanged), nausea 2 (unchanged), vomiting 0 (unchanged), cramps 1 (improved), diarrhea 0 (worsened [Reviewer comment: this is an error, since baseline diarrhea was rated as “3” which is severe.]).

16:10 Primary endpoint Q response: No; symptom intensities: pain 3 (severe, worse), nausea 2 (moderate, unchanged), vomiting 0 (none, unchanged), cramps 3 (severe, worse), diarrhea 0 (better; was originally rated 0, which was crossed and replaced with “1” which was crossed out and replaced with the original “0.”

16:30 Primary endpoint Q response: No; All symptoms grade 3 (severe, worse), except vomiting (none, unchanged). Change in vomiting score changed from no change to worse. One BM and no vomiting since last assessment.

16:50 Primary endpoint Q response: No; All symptoms grade 3 (severe, worse), except vomiting (none, unchanged). Change in vomiting

score changed from no change to worse. One BM and no vomiting since last assessment.

5 hour assessment not done.

6 hour assessment not done.

7 hour assessment not done.

8 hour assessment not done.

8 hour C1-INH and C4 levels not done

8 hour vital signs not done.

12 hour assessment not done.

12 hour C1-INH and C4 levels not done

Appendix 2 - Complete listings of all AEs by frequency and by organ system for the 4 hour safety population and for the “Overall Berinert P safety population (n = 108). The latter safety population appears to include all AEs reported in the low and high dose Berinert P arms plus AEs that began following infusion of Berinert as rescue medication in the Placebo arm.

Table 12.2: Incidence of adverse events by descending frequency - Four-hour-safety-population

| | Statistic | Placebo | Low dose Berinert | High dose Berinert | All Berinert |
|---------------------------------|-----------|----------|----------------------|-----------------------|--------------|
| Total number of subjects | N (%) | 41 (100) | 39 (100) | 46 (100) | 85 (100) |
| MedDRA - preferred term | | | | | |
| Nausea | N (%) | 5 (12.2) | 1 (2.6) | 3 (6.5) | 4 (4.7) |
| Muscle spasms | N (%) | 2 (4.9) | 4 (10.3) | 1 (2.2) | 5 (5.9) |
| Abdominal pain | N (%) | 3 (7.3) | 1 (2.6) | 2 (4.3) | 3 (3.5) |
| Pain | N (%) | 1 (2.4) | 4 (10.3) | 1 (2.2) | 5 (5.9) |
| Diarrhoea | N (%) | 4 (9.8) | 1 (2.6) | 0 | 1 (1.2) |
| Vomiting | N (%) | 3 (7.3) | 1 (2.6) | 1 (2.2) | 2 (2.4) |
| Dysgeusia | N (%) | 0 | 1 (2.6) | 2 (4.3) | 3 (3.5) |
| Headache | N (%) | 2 (4.9) | 1 (2.6) | 0 | 1 (1.2) |
| Face oedema | N (%) | 1 (2.4) | 1 (2.6) | 0 | 1 (1.2) |
| Lip swelling | N (%) | 1 (2.4) | 1 (2.6) | 0 | 1 (1.2) |
| Oedema peripheral | N (%) | 0 | 1 (2.6) | 1 (2.2) | 2 (2.4) |
| Abdominal distension | N (%) | 0 | 1 (2.6) | 0 | 1 (1.2) |
| Back pain | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Blood pressure increased | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Body temperature increased | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Dysphagia | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Dysphonia | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Eructation | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Facial pain | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Gastroesophageal reflux disease | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Muscle tightness | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Oedema mouth | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Pharyngolaryngeal pain | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Throat tightness | N (%) | 1 (2.4) | 0 | 0 | 0 |

Only AEs starting within 4 hours after start of infusion are taken into account.
 Low dose: >0 - 15 U/kg bw Berinert as treated, High dose: >15 U/kg bw Berinert as treated
 21DEC2007 / 9:18 / aaefreq.sas

Table 12.3: Incidence of adverse events grouped by SOC - Four-hour-safety-population

| System organ class Preferred term | Statistic | Placebo | Low dose Berinert | High dose Berinert | All Berinert |
|--|-----------|-----------|----------------------|-----------------------|--------------|
| Total number of subjects | N (%) | 41 (100) | 39 (100) | 46 (100) | 85 (100) |
| Total subjects with AEs | N (%) | 18 (43.9) | 10 (25.6) | 9 (19.6) | 19 (22.4) |
| Gastrointestinal disorders | N (%) | 13 (31.7) | 3 (7.7) | 5 (10.9) | 8 (9.4) |
| Abdominal distension | N (%) | 0 | 1 (2.6) | 0 | 1 (1.2) |
| Abdominal pain | N (%) | 3 (7.3) | 1 (2.6) | 2 (4.3) | 3 (3.5) |
| Diarrhoea | N (%) | 4 (9.8) | 1 (2.6) | 0 | 1 (1.2) |
| Dysphagia | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Eructation | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Gastrooesophageal reflux disease | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Lip swelling | N (%) | 1 (2.4) | 1 (2.6) | 0 | 1 (1.2) |
| Nausea | N (%) | 5 (12.2) | 1 (2.6) | 3 (6.5) | 4 (4.7) |
| Oedema mouth | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Vomiting | N (%) | 3 (7.3) | 1 (2.6) | 1 (2.2) | 2 (2.4) |
| General disorders and administration site conditions | N (%) | 3 (7.3) | 5 (12.8) | 2 (4.3) | 7 (8.2) |
| Face oedema | N (%) | 1 (2.4) | 1 (2.6) | 0 | 1 (1.2) |
| Facial pain | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Oedema peripheral | N (%) | 0 | 1 (2.6) | 1 (2.2) | 2 (2.4) |
| Pain | N (%) | 1 (2.4) | 4 (10.3) | 1 (2.2) | 5 (5.9) |
| Investigations | N (%) | 0 | 0 | 2 (4.3) | 2 (2.4) |
| Blood pressure increased | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Body temperature increased | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Musculoskeletal and connective tissue disorders | N (%) | 4 (9.8) | 4 (10.3) | 1 (2.2) | 5 (5.9) |
| Back pain | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Muscle spasms | N (%) | 2 (4.9) | 4 (10.3) | 1 (2.2) | 5 (5.9) |
| Muscle tightness | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Nervous system disorders | N (%) | 2 (4.9) | 2 (5.1) | 2 (4.3) | 4 (4.7) |
| Dysgeusia | N (%) | 0 | 1 (2.6) | 2 (4.3) | 3 (3.5) |
| Headache | N (%) | 2 (4.9) | 1 (2.6) | 0 | 1 (1.2) |
| Respiratory, thoracic and mediastinal disorders | N (%) | 2 (4.9) | 0 | 1 (2.2) | 1 (1.2) |
| Dysphonia | N (%) | 1 (2.4) | 0 | 0 | 0 |
| Pharyngolaryngeal pain | N (%) | 0 | 0 | 1 (2.2) | 1 (1.2) |
| Throat tightness | N (%) | 1 (2.4) | 0 | 0 | 0 |

Only AEs starting within 4 hours after start of infusion are taken into account.

Low dose: >0 - 15 U/kg bw Berinert as treated, High dose: >15 U/kg bw Berinert as treated

21DEC2007 / 9:21 / aaeinc.sas

Table 12.32: Incidence of adverse events by descending frequency - Overall Berinert P-safety-population

| Statistic | | Total Berinert P dose >0 to <=15 U/kg b.w. (incl. rescue study medication) | Total Berinert P dose > 15 U/kg b.w. (incl. rescue study medication) | All Berinert |
|--|-------|---|---|--------------|
| Total number of subjects | N (%) | 26 (100) | 82 (100) | 108 (100) |
| MedDRA - preferred term | | | | |
| Hereditary angioedema | N (%) | 4 (15.4) | 10 (12.2) | 14 (13.0) |
| Headache | N (%) | 1 (3.8) | 12 (14.6) | 13 (12.0) |
| Abdominal pain | N (%) | 1 (3.8) | 6 (7.3) | 7 (6.5) |
| Nausea | N (%) | 0 | 7 (8.5) | 7 (6.5) |
| Muscle spasms | N (%) | 0 | 6 (7.3) | 6 (5.6) |
| Pain | N (%) | 0 | 6 (7.3) | 6 (5.6) |
| Diarrhoea | N (%) | 0 | 5 (6.1) | 5 (4.6) |
| Vomiting | N (%) | 0 | 5 (6.1) | 5 (4.6) |
| Back pain | N (%) | 0 | 4 (4.9) | 4 (3.7) |
| Dysgeusia | N (%) | 1 (3.8) | 3 (3.7) | 4 (3.7) |
| Oedema peripheral | N (%) | 1 (3.8) | 3 (3.7) | 4 (3.7) |
| Abdominal distension | N (%) | 0 | 2 (2.4) | 2 (1.9) |
| Upper respiratory tract infection | N (%) | 1 (3.8) | 1 (1.2) | 2 (1.9) |
| Abdominal pain upper | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Anxiety | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Biliary colic | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Blood pressure increased | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Body temperature increased | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Bronchitis | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Cough | N (%) | 1 (3.8) | 0 | 1 (0.9) |
| Cystitis | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Dysphagia | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Ear pain | N (%) | 1 (3.8) | 0 | 1 (0.9) |
| Eructation | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Face oedema | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Haematuria | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Haemorrhoidal haemorrhage | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Influenza | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Joint swelling | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Lip swelling | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Pharyngolaryngeal pain | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Puncture site reaction | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Pyrexia | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| MedDRA - preferred term (continued) | | | | |
| Renal pain | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Retching | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Rhinorrhoea | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Tendonitis | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Throat irritation | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Toothache | N (%) | 0 | 1 (1.2) | 1 (0.9) |

Only AEs after first infusion of Berinert are taken into account.
21DEC2007 / 9:18 / aaefreq.sas

Table 12.33: Incidence of adverse events grouped by SOC - Overall Berinert P-safety-population

| System organ class Preferred term | Statistic | Total Berinert P dose >0 to <=15 U/kg b.w. (incl. rescue study medication) | Total Berinert P dose > 15 U/kg b.w. (incl. rescue study medication) | All Berinert |
|---|-----------|---|---|--------------|
| Infections and infestations | N (%) | 1 (3.8) | 4 (4.9) | 5 (4.6) |
| Bronchitis | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Cystitis | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Influenza | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Upper respiratory tract infection | N (%) | 1 (3.8) | 1 (1.2) | 2 (1.9) |
| Investigations | N (%) | 0 | 2 (2.4) | 2 (1.9) |
| Blood pressure increased | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Body temperature increased | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Musculoskeletal and connective tissue disorders | N (%) | 0 | 11 (13.4) | 11 (10.2) |
| Back pain | N (%) | 0 | 4 (4.9) | 4 (3.7) |
| Joint swelling | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Muscle spasms | N (%) | 0 | 6 (7.3) | 6 (5.6) |
| Tendonitis | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Nervous system disorders | N (%) | 2 (7.7) | 13 (15.9) | 15 (13.9) |
| Dysgeusia | N (%) | 1 (3.8) | 3 (3.7) | 4 (3.7) |
| Headache | N (%) | 1 (3.8) | 12 (14.6) | 13 (12.0) |
| Psychiatric disorders | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Anxiety | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Renal and urinary disorders | N (%) | 0 | 2 (2.4) | 2 (1.9) |
| Haematuria | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Renal pain | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Respiratory, thoracic and mediastinal disorders | N (%) | 1 (3.8) | 3 (3.7) | 4 (3.7) |
| Cough | N (%) | 1 (3.8) | 0 | 1 (0.9) |
| Pharyngolaryngeal pain | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Rhinorrhoea | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Throat irritation | N (%) | 0 | 1 (1.2) | 1 (0.9) |

Only AEs after first infusion of Berinert are taken into account.

Table 12.34: Incidence of possibly related adverse events grouped by SOC - Overall Berinert P-safety-population

| System organ class Preferred term | Statistic | Total Berinert P dose >0 to ≤15 U/kg b.w. (incl. rescue study medication) | Total Berinert P dose > 15 U/kg b.w. (incl. rescue study medication) | All Berinert |
|---|-----------|--|---|--------------|
| Total number of subjects | N (%) | 26 (100) | 82 (100) | 108 (100) |
| Total subjects with AEs | N (%) | 1 (3.8) | 28 (34.1) | 29 (26.9) |
| Congenital, familial and genetic disorders | N (%) | 0 | 3 (3.7) | 3 (2.8) |
| Hereditary angioedema | N (%) | 0 | 3 (3.7) | 3 (2.8) |
| Gastrointestinal disorders | N (%) | 0 | 14 (17.1) | 14 (13.0) |
| Abdominal distension | N (%) | 0 | 2 (2.4) | 2 (1.9) |
| Abdominal pain | N (%) | 0 | 5 (6.1) | 5 (4.6) |
| Diarrhoea | N (%) | 0 | 4 (4.9) | 4 (3.7) |
| Dysphagia | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Eructation | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Lip swelling | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Nausea | N (%) | 0 | 6 (7.3) | 6 (5.6) |
| Retching | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Vomiting | N (%) | 0 | 4 (4.9) | 4 (3.7) |
| Haemorrhoidal haemorrhage | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| General disorders and administration site conditions | N (%) | 0 | 7 (8.5) | 7 (6.5) |
| Oedema peripheral | N (%) | 0 | 2 (2.4) | 2 (1.9) |
| Pain | N (%) | 0 | 5 (6.1) | 5 (4.6) |
| Pyrexia | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Infections and infestations | N (%) | 0 | 2 (2.4) | 2 (1.9) |
| Cystitis | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Influenza | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Investigations | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Body temperature increased | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Musculoskeletal and connective tissue disorders | N (%) | 0 | 7 (8.5) | 7 (6.5) |
| Back pain | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Joint swelling | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Muscle spasms | N (%) | 0 | 6 (7.3) | 6 (5.6) |
| Only AEs after first infusion of Berinert are taken into account. | | | | |
| Nervous system disorders | N (%) | 1 (3.8) | 8 (9.8) | 9 (8.3) |
| Dysgeusia | N (%) | 1 (3.8) | 3 (3.7) | 4 (3.7) |
| Headache | N (%) | 0 | 6 (7.3) | 6 (5.6) |
| Psychiatric disorders | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Anxiety | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Renal and urinary disorders | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Haematuria | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Respiratory, thoracic and mediastinal disorders | N (%) | 0 | 1 (1.2) | 1 (0.9) |
| Throat irritation | N (%) | 0 | 1 (1.2) | 1 (0.9) |

Table 12.35: Severity of adverse events by SOC- Overall Berinert P-safety-population

| System organ class Preferred term | Total Berinert P dose >0 to <=15 U/kg b.w. (incl. rescue study medication) (n= 26) | | | Total Berinert P dose > 15 U/kg b.w. (incl. rescue study medication) (n= 82) | | | All Berinert (n= 108) | | |
|---|--|----------|----------|---|----------|----------|-----------------------|----------|----------|
| | Severity | | | Severity | | | Severity | | |
| | mild | moderate | severe | mild | moderate | severe | mild | moderate | severe |
| Infections and infestations | 0 | 0 | 1 (3.8) | 0 | 3 (3.7) | 1 (1.2) | 0 | 3 (2.8) | 2 (1.9) |
| Bronchitis | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Cystitis | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Influenza | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Upper respiratory tract infection | 0 | 0 | 1 (3.8) | 0 | 0 | 1 (1.2) | 0 | 0 | 2 (1.9) |
| Investigations | - | - | - | 2 (2.4) | 0 | 0 | 2 (1.9) | 0 | 0 |
| Blood pressure increased | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Body temperature increased | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | - | - | - | 2 (2.4) | 6 (7.3) | 3 (3.7) | 2 (1.9) | 6 (5.6) | 3 (2.8) |
| Back pain | - | - | - | 1 (1.2) | 3 (3.7) | 0 | 1 (0.9) | 3 (2.8) | 0 |
| Joint swelling | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Muscle spasms | - | - | - | 1 (1.2) | 2 (2.4) | 3 (3.7) | 1 (0.9) | 2 (1.9) | 3 (2.8) |
| Tendonitis | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Nervous system disorders | 2 (7.7) | 0 | 0 | 9 (11.0) | 5 (6.1) | 1 (1.2) | 11 (10.2) | 5 (4.6) | 1 (0.9) |
| Dysgeusia | 1 (3.8) | 0 | 0 | 3 (3.7) | 0 | 0 | 4 (3.7) | 0 | 0 |
| Headache | 1 (3.8) | 0 | 0 | 6 (7.3) | 5 (6.1) | 1 (1.2) | 7 (6.5) | 5 (4.6) | 1 (0.9) |
| Psychiatric disorders | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Anxiety | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Renal and urinary disorders | - | - | - | 1 (1.2) | 0 | 1 (1.2) | 1 (0.9) | 0 | 1 (0.9) |
| Haematuria | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Renal pain | - | - | - | 0 | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) |
| Respiratory, thoracic and mediastinal disorders | 1 (3.8) | 0 | 0 | 2 (2.4) | 1 (1.2) | 0 | 3 (2.8) | 1 (0.9) | 0 |
| Cough | 1 (3.8) | 0 | 0 | - | - | - | 1 (0.9) | 0 | 0 |
| Pharyngolaryngeal pain | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Rhinorrhoea | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Throat irritation | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |

Table 12.36: Severity of possibly related adverse events by SOC - Overall Berinert P-safety-population

| System organ class Preferred term | Total Berinert P dose >0 to <=15 U/kg b.w. (incl. rescue study medication) (n= 26) | | | Total Berinert P dose > 15 U/kg b.w. (incl. rescue study medication) (n= 82) | | | All Berinert (n= 108) | | |
|--|--|----------|--------|---|-----------|----------|-----------------------|-----------|----------|
| | Severity | | | Severity | | | Severity | | |
| | mild | moderate | severe | mild | moderate | severe | mild | moderate | severe |
| Total patients with adverse events | 1 (3.8) | 0 | 0 | 15 (18.3) | 15 (18.3) | 8 (9.8) | 16 (14.8) | 15 (13.9) | 8 (7.4) |
| Congenital, familial and genetic disorders | - | - | - | 0 | 2 (2.4) | 1 (1.2) | 0 | 2 (1.9) | 1 (0.9) |
| Hereditary angioedema | - | - | - | 0 | 2 (2.4) | 1 (1.2) | 0 | 2 (1.9) | 1 (0.9) |
| Gastrointestinal disorders | - | - | - | 8 (9.8) | 5 (6.1) | 6 (7.3) | 8 (7.4) | 5 (4.6) | 6 (5.6) |
| Abdominal distension | - | - | - | 1 (1.2) | 0 | 1 (1.2) | 1 (0.9) | 0 | 1 (0.9) |
| Abdominal pain | - | - | - | 2 (2.4) | 1 (1.2) | 2 (2.4) | 2 (1.9) | 1 (0.9) | 2 (1.9) |
| Diarrhoea | - | - | - | 3 (3.7) | 1 (1.2) | 0 | 3 (2.8) | 1 (0.9) | 0 |
| Dysphagia | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Erectation | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Haemorrhoidal haemorrhage | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Lip swelling | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Nausea | - | - | - | 1 (1.2) | 2 (2.4) | 3 (3.7) | 1 (0.9) | 2 (1.9) | 3 (2.8) |
| Retching | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Vomiting | - | - | - | 1 (1.2) | 1 (1.2) | 2 (2.4) | 1 (0.9) | 1 (0.9) | 2 (1.9) |
| General disorders and administration site conditions | - | - | - | 2 (2.4) | 2 (2.4) | 4 (4.9) | 2 (1.9) | 2 (1.9) | 4 (3.7) |
| Oedema peripheral | - | - | - | 1 (1.2) | 1 (1.2) | 0 | 1 (0.9) | 1 (0.9) | 0 |
| Pain | - | - | - | 1 (1.2) | 0 | 4 (4.9) | 1 (0.9) | 0 | 4 (3.7) |
| Pyrexia | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Infections and infestations | - | - | - | 0 | 2 (2.4) | 0 | 0 | 2 (1.9) | 0 |
| Cystitis | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Influenza | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Investigations | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Body temperature increased | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | - | - | - | 1 (1.2) | 3 (3.7) | 3 (3.7) | 1 (0.9) | 3 (2.8) | 3 (2.8) |
| Back pain | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Joint swelling | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Muscle spasms | - | - | - | 1 (1.2) | 2 (2.4) | 3 (3.7) | 1 (0.9) | 2 (1.9) | 3 (2.8) |
| Nervous system disorders | 1 (3.8) | 0 | 0 | 5 (6.1) | 3 (3.7) | 1 (1.2) | 6 (5.6) | 3 (2.8) | 1 (0.9) |
| Dysgeusia | 1 (3.8) | 0 | 0 | 3 (3.7) | 0 | 0 | 4 (3.7) | 0 | 0 |
| Headache | - | - | - | 2 (2.4) | 3 (3.7) | 1 (1.2) | 2 (1.9) | 3 (2.8) | 1 (0.9) |
| Psychiatric disorders | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Anxiety | - | - | - | 0 | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 |
| Renal and urinary disorders | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Haematuria | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |
| Throat irritation | - | - | - | 1 (1.2) | 0 | 0 | 1 (0.9) | 0 | 0 |

Only AEs after first infusion of Berinert are taken into account.

Appendix 3 - Review of Sponsor Responses to 20 December 2007 CBER IND Information Request Letter

Upon submission of a synopsis of the study results to the IND as amendment 50 in late 2007, the following were communicated in writing to the sponsor by letter dated 20 December 2007. The sponsor's responses, contained in original BLA module 1, attachment 2, are indicated in italics after each numbered item from the FDA information request, together with my reviewer comments in bold:

1. Please submit the raw data for study CE1145_3001 at this time to the IND, including databases that are specific to individual study sites. Please also submit a list of all study site investigators, addresses, and telephone numbers at this time.

Sponsor's response:

This was submitted to the IND on 21 Dec 2007 and is in BLA CD-ROM for study CE1145_3001. Clinical investigator information is in Module 1, Section 1.3.4.

Reviewer Comment on Sponsor Response:

Noted.

2. Please reconcile the statement in the submission that the cut-off date for the analyses was 29 June 2007, yet the last subject did not complete the final day 7-9 visit until 2 October 2007.

Sponsor's response:

The cut-off date of 9 June 2007 was for continuation study CE1145_3003, not for CE1145_3001.

Reviewer Comment on Sponsor Response:

Noted.

3. Please submit with the BLA an analysis comparing treatment groups in terms of time from onset of the attack to time to initial relief of attack symptoms.

Sponsor's response:

The requested analysis is in Module 5, section 5.3.5.1.1-3.2.

The sponsor notes that for the Berinert P 20 U/kg group, the mean and median time intervals between start of attack and initiation of treatment was longer than the same interval for the placebo group (median 6.0 vs.

5.3 hours, mean 11.4 vs. 8.7 hours, respectively, in the ITT analysis (Table Q.3.1.1.c).

The sponsor undertook an additional analysis of the time when the attack became moderate or severe to the time of onset of relief of symptoms. According to this sponsor-generated post-hoc analysis, the treatment effect and p value of statistical significance were similar to that seen in the primary analysis (Table Q3.3.1b)

The sponsor has also provided a post-hoc analysis similar to those above but without setting a poor/failure outcome for the cases where rescue study medication or analgesics or anti-emetics or open label C1-INH were administered before a primary endpoint event was otherwise reached (i.e., before time to start of relief of HAE symptoms).

Reviewer Comment on Sponsor Response:

This difference between randomization groups in the time from start of attack and administration of CTM is in the direction which would tend to exaggerate the observed benefit of the Berinert P group over the placebo group, given that all attacks are self-limited and end eventually even without intervention.. It is noteworthy that the magnitude of this median between-treatment-group difference from start of attack until the time the test article is given is of the same order as the between-treatment-group difference in the primary endpoint (time interval from administration of CTM to start of relief of symptoms. This tends to diminish somewhat the sponsor's conclusion that the administration of the test product was responsible for the apparent better primary endpoint outcome for the test group. However, the difference between the means between high dose and placebo groups in the time from start of attack to start of resolution of symptoms of HAE attack is statistically significant, using the sponsor's imputation method for subjects who received any rescue medication.

Sponsor Table Q3.1.1 in Module 5, Section 5. 3.5.1.1- shows that in the sponsor's analysis of time from start of attack to start of relief of symptoms, an imputed time of 96 hours was assigned for subjects to received rescue study medication after 4 hours from start of treatment or analgesics/anti-emetics/open-label C1-INH/FFP during the first 4 hours. The mean, median, and SDs for these times by group are given below:

Time Interval in Hours in ITT population

| Randomization Group: | Berinert P 20 U/kg | Placebo |
|-----------------------------|---------------------------|----------------|
| Number of Subjects | 43 | 42 |
| Mean | 24.2 | 44.6 |
| Median | 7.8 | 11.5 |
| Standard Deviation | 33.0 | 43.5 |

Ten subjects (2%) in the Berinert P 20 U/kg group, 13 subjects (3%) in the 10 U/kg group, and 25 subjects (60%) in the placebo group received any rescue medication.

The 20.4 hour difference between the means in the time from start of attack to start of relief of symptoms for the high dose and placebo groups (24.2 hours minus 44.6 hours equals minus 20.4 hours) is significant with a 2-sided p value of 0.0146 (email communication from ---b(4)-----, 25 March 2008 at 1:48 PM). The sponsor's 1-sided p value for the differences between the high dose and placebo group in time from start of attack to start of resolution of symptoms (normal approximation) for the ITT population was 0.024 and for the per-protocol population was 0.023. For the ITT population the log rank test gave a 2-sided p value of 0.035. Using a closed testing procedure, the p value for the difference between low and high dose groups by Wilcoxon rank sum test was 0.04 in the ITT population. The treatment effect estimate for high dose vs. placebo was -2.08 hours with 95% CI from -12.917 to 0.0.

Rather similar results for mean time from onset of attack to start of relief of symptoms was seen for the per protocol (PP) population; however, for the PP population, the difference in median times was less (5.33 vs. 5.08 vs. 4.40 hours in placebo, low dose, and high dose Berinert P groups, respectively).

Interestingly, the superior results for Berinert P vis-à-vis placebo for time from onset of attack to time to initial relief of symptoms was totally dependent on imputing 96 hour values for those subjects who were given any kind of rescue medication (C1-INH, FFP, or analgesics) prior to reaching this endpoint. This can be seen in the following, excerpted from sponsor Table Q3.2.1:

Time Interval in Hours (ITT, ignoring any use of rescue medication

| Randomization Group: | Berinert P 20 U/kg | Berinert P 10 U/kg | Placebo |
|-----------------------------|---------------------------|---------------------------|----------------|
| Number of Subjects | 43 | 39 | 42 |
| Mean | 12.7 | 11.0 | 11.1 |
| Median | 7.2 | 8.4 | 8.2 |
| Standard Deviation | 15.6 | 6.6 | 9.4 |

The time interval from when the attack became moderate/severe and onset of initial relief of symptoms is given in the following table, excerpted from sponsor's Table Q3.1.1b (an imputed value of 96 hours was chosen by the sponsor and used for subjects who received any rescue type medication, as in the prior analysis. The sponsor

states they chose 94 hours rather than the 24 hour imputed corresponding value for the primary endpoint because some subjects had a delay of more than 24 hours (up to 86.75 hours) between onset of attack and start of study medication):

Time Interval in Hours

| Randomization Group: | Berinert P 20 U/kg | Placebo |
|-----------------------------|---------------------------|----------------|
| Number of Subjects | 43 | 42 |
| Mean | 16.9 | 41.4 |
| Median | 4.5 | 5.4 |
| Standard Deviation | 32.2 | 45.5 |

The time interval from when the start of the attack and onset of the administration of study test medication is given in the following table, excerpted from sponsor's Table Q3.1.1c

Time Interval in Hours

| Randomization Group: | Berinert P 20 U/kg | Berinert P 10 U/kg | Placebo |
|-----------------------------|---------------------------|---------------------------|----------------|
| Number of Subjects | 43 | 39 | 42 |
| Mean | 11.4 | 9.2 | 8.6 |
| Median | 6.0 | 6.5 | 5.3 |
| Standard Deviation | 15.5 | 6.6 | 8.9 |

The time interval from when the start of the attack and onset of the administration of study test medication is given in the following table, excerpted from sponsor's Table Q3.1.1c

Time Interval in Hours

| Randomization Group: | Berinert P 20 U/kg | Berinert P 10 U/kg | Placebo |
|-----------------------------|---------------------------|---------------------------|----------------|
| Number of Subjects | 43 | 39 | 42 |
| Mean | 3.43 | 3.42 | 3.39 |
| Median | 3.50 | 3.72 | 3.25 |
| Standard Deviation | 1.09 | 1.09 | 1.04 |

Time Interval in Hours

| Randomization Group: | Berinert P 20 U/kg | Berinert P 10 U/kg | Placebo |
|-----------------------------|---------------------------|---------------------------|----------------|
| Number of Subjects | 43 | 39 | 42 |
| Mean | | | |
| Median | | | |
| Standard Deviation | | | |

4. Please submit with the BLA a modified robustness analysis of the primary endpoint which does not treat as responders subjects who report initial relief of HAE attack symptoms as of the initial 15 minute post-dose assessment timepoint.

Sponsor's response:

The sponsor excluded from this analysis subjects whose time to initial relief of symptoms was ≤ 15 min. Analysis results are in Module 5, section 6.3.5.1 - .3. The analysis was done with and without setting a poor/failure outcome for subjects who received rescue study medication/analgesics/anti-emetics/open-label C1-INH before time of start of relief.

Reviewer Comment on Sponsor Response:

ITT analysis results for time from CTM administration to time to initial relief of HAE attack symptoms is given in the following table, abstracted from Sponsor's Table Q4.1.1. The time was set to 24 hours for subjects receiving any rescue type medication.

Time Interval in Hours

| Randomization Group: | Berinert P 20 U/kg | Berinert P 10 U/kg | Placebo |
|--|---------------------------|---------------------------|----------------|
| Number of Subjects Randomized | 43 | 39 | 42 |
| Number of Subjects Analyzed | 34 | 34 | 37 |
| Number of Subjects Excluded from Analysis | 9 | 5 | 5 |
| Mean | 4.9 | 8.5 | 11.6 |
| Median | 0.82 | 1.48 | 3.00 |
| Standard Deviation | 9.0 | 10.9 | 11.6 |

The 1-sided p values (normal approximation) for the difference between high dose and placebo for the ITT and per-protocol populations were 0.003 and 0.002, respectively. The log-rank 2-sided p values were 0.015 and 0.010, respectively. The low and high dose groups were also statistically significantly different from each other in ITT, PP, and ePP populations (see next Question).

The following table is analogous to the one above, but ignores "potential rescue medication."

| Randomization Group: | Berinert P 20 U/kg | Berinert P 10 U/kg | Placebo |
|--|---------------------------|---------------------------|----------------|
| Number of Subjects Randomized | 43 | 39 | 42 |
| Number of Subjects Analyzed | 33 | 32 | 36 |
| Number of Subjects Excluded from Analysis | 10 | 7 | 6 |
| Mean | 1.4 | 2.2 | 2.7 |
| Median | 0.8 | 1.3 | 2.4 |
| Standard Deviation | 1.6 | 1.9 | 2.0 |

5. Please reconcile your statements that 125 subjects were randomized, yet the intent-to-treat (ITT) analysis population comprises only 124 subjects.

Sponsor's response:

There were 127 admissions to the study. One subject was admitted twice to the study under subject ID numbers ---b(6)------. Thus, there were 126 unique subjects admitted to the study. Subject -b(6)- was not randomized but received study medication.

The number of subjects randomized was 125. Subject -b(6)-- was randomized to C1-INH 10 U/kg group, but did not receive any blinded study medication. Rather, this subject received open-label emergency study product because laryngeal edema developed before the blinded study medication could be started. The subject did not meet the protocol-stated definition for inclusion in the ITT analysis because it was to include only "...subjects to received any portion of the study medication."

The sponsor has included 2 sets of data sets that both include and exclude subject -b(6)-.

Reviewer Comment on Sponsor Response:

As noted during review of the IND, the what the sponsor calls an ITT population is really a modified ITT population.

6. Why did the median dose of Berinert P in group 3 increase from 1400 total Units to 1420 U after rescue medication was included?

Sponsor's response:

Subjects --b(6)----- both received open-label emergency C1-INH (20 U/kg) for laryngeal attacks, in addition to the initial 20 U/kg dose of CTM. Subject -b(6)- received the open label treatment 13 days after complete resolution of the study attack.

Reviewer Comment on Sponsor Response:

Noted.

7. Please analyze and present in the BLA by group “as treated” the proportion of subjects reporting (a) any AEs, (b) AEs starting within 72 hours of product administration and (c) AEs starting within 72 hours of product administration and/or considered at least possibly related to administration of study article.

Sponsor’s response:

The sponsor has not properly addressed FDA’s request to analyze AEs according to their temporal relationship to infusions (i.e., AEs starting within during or within 72 hours of the start of any (including rescue) infusion). Rather, Inspection of the tables submitted in partial response to this item reveals that only AEs that occurred during or within 72 hours of the initial infusion of study product were included in these analyses, which was not the intent of the CBER question. the sponsor responds that:

AE analyses were conducted in 3 study populations defined in the protocol:

- The 4 hour safety population taking all AEs into account (instead of only those within the first 4 hours after the start of initial dose of study medication as done in the primary analysis in the CSR).*
- The after 4-hour safety population without rescue medication taking all AEs of these subjects into account (instead of only those within the first 4 hours after the start of initial dose of study medication as done in the primary analysis in the CSR).*
- The after 4 hour safety population with rescue study medication taking all AEs of these subjects into account (instead of only those within the first 4 hours after the start of initial dose of study medication as done in the primary analysis in the CSR).*

All these populations are “as treated” populations as defined in the protocol.

Note: There is no analysis of a population comparing subjects who received any dose of C1-INH to subjects who received only placebo. This analysis would not be appropriate [in the sponsor’s view] for the C1-INH group as subjects randomized to placebo, but receiving c1-INH as rescue medication would presumably tend to be those with more AEs than those in the placebo group for whom it was not necessary to administer rescue study medication. If in this analysis subjects in the placebo group receiving rescue study medication after 4 hours was [sic] taken into account for the placebo group with their 4-hour time period, this would result in another inappropriate comparison as the observation time for AEs would be shorter than for those subjects receiving any CVI-INH.

Reviewer Comment on Sponsor Response:

The sponsor should submit analyses of (1) all AEs, (2) AEs judged by the investigator or sponsor to be at least possibly related to administration of test article (or beginning within 72 hours of the start of any administration of rescue study medication), and (3) all AEs minus those compatible with being symptoms of an HAE attack by 4 hour time intervals (including separate and cumulative intervals in 4 hour increments, i.e, 0-4, 4-8, 0-8, 8-12, 0-12, 12-16, 0-16 hours, etc), comparing (a) subjects randomized to receive Berinert P 20 U/kg and (b) subjects randomized to placebo, with censoring of AE data as of the time they may have received rescue study medication or open-label Berinert P. The sponsor should perform and submit these analyses for both all AEs and for all AEs that began during or within 72 hours of the start of any infusion of product. As agreed during the IND stage, all AEs reported within 72 hours of any administration of rescue study medication are to be classified as possibly related to Berinert P administration. Do not classify AEs that begin more than 72 hours following Berinert P administration but begin during or up to 72 hours of placebo rescue medication as at least possibly product related. In addition, please provide the results of pooled analyses of AEs from the initial 4 hours in the high dose randomization group combined with AEs that occur during the 4 hours following blinded administration of 20 U/kg rescue Berinert P and compare these to the incidence of AEs that occur in the placebo group during the initial 4 hours (with and without subtraction of AEs that are compatible with being due to an HAE attack). In addition, perform a similar pooled comparison of AEs without restriction as to time frame of observation, except for censoring those AEs that follow administration of rescue Berinert P (either blinded or open label). This analysis should be done with and without correction for the number of subject-hours of in-hospital observation. These analyses should also be done pooled and separately for the subgroups of AEs classified as mild, moderate, and severe in intensity.

In addition, please provide expanded definitions of the 3 numbered safety analysis populations cited in your response to this question. Given that study populations 1) and 2) both are stated to represent “all AEs” the difference between these 2 safety analysis populations is somewhat ambiguous.

The tables referenced in your response to question 7 of our 20 December 2007 letter, as contained in Attachment 2 of Module 1, volume 1 (“Module 5, Tables Q7.1 to Q7.3), state in a footnote that they include only “AEs starting during infusion and within 72 hours after end of initial [emphasis added] study drug infusion are taken into account.” Please redo these tables including AEs starting during or within 72 hours of either the initial or subsequent (e.g., study rescue medication) infusions of test article.

For each analysis of AEs, please provide, in addition to summary statistics, a table listing the output of each analysis in terms of lists by

treatment/treatment group of each AE (preferred and verbatim term) with time of onset and severity, as well as a table totally AEs by body system and by preferred term. Please include -b(4)- code for all AE analyses in your submission.

8. Please analyze and present in the BLA an intent-to-treat analysis of (a) all AEs, (b) AEs other than those compatible with HAE symptoms, and (c) AEs deemed at least possibly related to administration of study product that occur within 72 hours following the initial administration of blinded study product.

Sponsor's response:

The sponsor states these additional analyses of AEs for the ITT population were conducted in the same manner as data was analyzed for the different safety populations in the primary safety analyses. The ITT population is identical with the ITT population used for the primary efficacy analysis.

- *The percentage of subjects with AEs was higher in the Placebo group than in the C1-INH 10 or 20 U/kg groups (Table Q8.1.1)*
- *The percentages of subjects with AEs other than those compatible with HAE symptoms were balanced between treatment groups (Table 8.2.1)*
- *The percentage of subjects with AEs at least possibly related to study drug was higher in the Placebo group than in the C1-INH 10 or 20 U/kg groups (Table Q8.3.1).*

The treatment group labels only refer to the initially randomized treatment.

See tables Q8.1.1 – Q8.3.9.

Reviewer Comment on Sponsor Response:

Please submit a list of those HAE-compatible symptoms which you removed from you analyses submitted in response to item 8(b).

In table Q8.1.4, have you included all AEs reported during or within 72 hours of the initial infusion of test article in response to item 8(c)? Throughout the BLA, whenever you state “possibly related adverse events” have you included all AEs that started during or within 72 hours of any infusion of test product, regardless of whether it was blinded or given open label? Did you also include AEs that started during or within 72 hours of blinded placebo rescue medication?

9. You tables of summary statistics provided as attachments to the submission state “Final analysis as of 14Nov2007 database close) – under validation.” Please explain what validation procedures had not yet been completed with respect to the submitted tables/analyses.

Sponsor's response:

There is no general answer for all delivered analyses as analyses would usually be in a different validation status. At the time of the 14 November 2007 IND amendment the validation of programs had not been finalized at --b(4)---; however, the primary analysis of the primary efficacy analysis was completely validated; all analyses were performed on the validated and closed database. Programs generating analyses sent on 21 December 2007 had undergone final validation.

Reviewer Comment on Sponsor Response:

Noted. CBER should verify whether, as a result of programming validation, any results presented in the IND changed when the same data were submitted in the BLA.

10. Please provide in the BLA efficacy analyses stratified by attack severity at baseline.

Sponsor's response:

For the primary endpoint, the p value of the stratified analysis using the -----b(4)-----
-----) was below that for the primary analysis ($p = 0.0015$ vs. $p = 0.0025$, respectively). No difference in treatment effect between moderate and severe attacks could be confirmed (test for interaction between treatment group and severity, $p = 0.46$).

Reviewer Comment on Sponsor Response:

Noted. The trial evidently provides no evidence that efficacy differs significantly between moderate and severe HAE attacks.

11. Please define the “ePP” study population.

Sponsor's response:

The protocol defined the epp (Exploratory Per-protocol) population in section 7.1 as follows:

The following subjects will be excluded from an additional ‘exploratory per-protocol’ population:

- *All subjects excluded from the PP population*
- *Subjects proven not to have HAE*
- *Subjects included who had neither an abdominal or facial attack, or who had only a mild severity attack.*

- *Subjects included despite meeting the following exclusion criteria:*
 - i. *Hx of hypersensitivity to study medication*
 - ii. *Treatment with any other investigational drug (except those for acute angioedema) within 30 days*
 - iii. *Treatment with FFP or native plasma within 7 days before start*
 - iv. *Use of narcotic pain meds and/or anti-emetics etween start of attack and administration of study medication.*
 - v. *Prior inclusion in the study*
 - vi. *Treatment with ACE inhibitors within 4 weeks of study start.*

Reviewer Comment on Sponsor Response:

Noted.

12. Please submit with the BLA an analysis of individual AEs, sorted by (a) organ system and (b) preferred term in combination with severity rating.

Sponsor's response:

These are provided in Module 5 as noted and were submitted to the IND on 21 December 2007.

Reviewer Comment on Sponsor Response:

Noted.

13. Please explain why there were 3 used of open label Berinert P or blinded rescue medication given prior to 4 hours when throat tightness was reported for only 1 subject.

Sponsor's response:

- *Subject -b(6)- received "emergency" study medication 2 hours after receiving C1-INH blinded study medication. "According to the monitor the patient had a facial attack and then later developed some throat tightness. The investigator could not diagnose or see any throat tightness, but since the subject complained about it, the investigator thought that it was appropriate to administer emergency open label product. Therefore, this was not an AE."*
- *Subject -b(6)- received emergency medication without receiving the randomized study medication 10 U/kg because the subject developed a laryngeal attack between randomization and planned administration of the study drug. For this subject "laryngeal edema" and "throat irritation" are documented as AEs.*

- *Subject -b(6)- (placebo group) received blinded rescue medication 1 hour and 40 minutes after the start of study medication. “This was earlier than planned in the protocol [i.e., a significant protocol violation]. The documented AE was sore throat (Preferred term: pharyngolaryngeal pain). “It can be assumed that the subject should have received open-label emergency C1-INH medication instead of blinded rescue medication.*

Reviewer Comment on Sponsor Response:

Please reclassify as an AE the “throat tightness” that resulted in open label study medication being administered hours after subject-b(6)- had received C1-INH blinded study medication due to this AE. Please explain your logic on not originally assigning this event as an AE.

Please remove “laryngeal edema” and “throat tightness” for subject -b(6)- which began prior to product administration from the list of “as treated” AEs unless either of these AEs worsened in intensity following administration of Berinert P.

We do not understand why you state in your response that subject -b(6)- “should have received open-label emergency C1-INH medication...” From your narrative description of this patient who developed a “sore throat” there appears to be no documentation that this protocol violation early administration of blinded study rescue medication was actually an emergency. Please comment.

14. Please submit to the IND and BLA electronic copies of the CRFs of all subjects who discontinued prematurely, received open label Berinert P, and/or had serious AEs.

Sponsor’s response:

These were submitted to the IND on 21 December 2007. See section 5.3.7, Appendix 16.3 for the 3001 study report.

Reviewer Comment on Sponsor Response:

Noted.

15. Please provide in the BLA a table of listing the subject ID numbers of all subjects who had reported any GI or facial/lip/mouth swelling adverse event

Sponsor’s response:

A line listing as requested is provided in Table Q15. Additional data are in Module 5, Appendix 16.2.7.18 of the CSR.

Reviewer Comment on Sponsor Response:

Noted.

16. Please employ unique subject ID numbers for all subjects across all studies for which you submit data in the BLA.

Sponsor's response:

A subject listing in Module 5, Listing L1, section 5.3.5.3.2 contains subject IDs for both the pivotal _3001 and _3003 extension studies, from which subject IDs across studies can be followed.

Reviewer Comment on Sponsor Response:

Noted. Although in Module 5.3.5.3.2-1 the APPENDIX I on p 20 of 23 of the “Statistical Analysis Concept – SAP pooled for 3001_3003” - “subject link list for subjects in both trials” is missing and states “(to be added), Module 5.3.5.2-8 L1 lists subject ID numbers side by side for the pivotal trial and its extension study. Different subject numbers were used for each trial.

17. Please assure that the adverse event databases submitted with the BLA contain fields for randomized treatment group identification and for “as treated” status, as well as for the date and time of onset of each AE, the date and time of completion of the preceding study product infusion, and the time difference in hours between the end of the prior infusion and the start of the AE (set to zero for AEs that began during an infusion).

Sponsor's response:

The data set ADAE submitted to the IND 21 December 2007 contains “most of the requested variables.”

Following this request, an additional data set ADAEFDA was created with all requested variables. The document describing ADAEFDA and derivation rules for additional variables is provided along with the data set in Module 5, section 5.3.5.1.1-3.1.

Reviewer Comment on Sponsor Response:

Noted. I may have further comments on the sponsor's response once the definition of field name variables list is received from the sponsor.

18. When describing analyses related to the proportion of subjects who received rescue medication, please always specify whether this includes analgesics or is limited to blinded rescue medication.

Sponsor's response:

“Any rescue medication” and “rescue medication” indicate any of the following:

- *Blinded rescue study medication*
- *Analgesics*
- *Anti-emetics*
- *Open-label C1-INH as emergency medication after start of study treatment*

“Rescue study medication” refers only to blinded rescue medication administered 4 or more hours after the start of study treatment.

Reviewer Comment on Sponsor Response:

Noted.

19. Please include the results of each interim analysis with the BLA.

Sponsor's response:

These, as well as DSMB meeting minutes, are in Module 5.3.5.1.1.

Reviewer Comment on Sponsor Response:

Noted.

APPENDIX 4

REVIEW OF SPONSOR AMENDMENT 6 DATED 15 May 2008 (RESPONSES TO CBER INFORMATION REQUEST FAXES TO SPONSOR DATED 16, 21, AND 23 APRIL 2008)

The following are elements of CBER's 16 2008 information request fax, the sponsor's responses in italics, and my reviewer comments on those responses in bold:

1. The membership of the DSMB (Module 5- vol 9 of 29, section 5.3.5.1.1.1.18) in the DSMB Charter states that one of the DSMB members is Dr. Wolfhart Kreuz. Please clarify if this is the same person as Dr. W. Kreuz who did the PK study, CE1145_ 2001.

Sponsor's Response:

Privatdozent W. Kreuz was the coordinating investigator of the submitted PK study and he was a DSMB member for the 3001 pivotal study. CSLB believes that this is not an issue.

Reviewer Comment:

BiMo may comment. Having a DSMB member who has been an investigator of the product being studied seems less than ideal.

2. Section 3.1 of the Charter states that there are 3 DSMB members. However, section 5.1 (Closed Sessions) of the Charter states that “All four members have one vote each”. Please clarify.

Sponsor’s Response:

There were only 3 DSMB members.

Reviewer Comment:

Noted.

3. Please indicate the database where the “Investigator Comments” is located in the BLA submission.

Sponsor’s Response:

Investigator comments used for analysis were included in analysis data files, eg. Variable AEINVCMT in data set ADAE in the BLA. A full set of investigator comments, exception values and general comments was included as datasets OCICMT, OCEXVAL and OCGCMT respectively in the amendment sent 30 April 2008.

Reviewer Comment:

Noted.

4. Item 7 from 20 Dec 2007 CBER letter:

Please analyze and present in the BLA by group “as treated” the proportion of subjects reporting (a) any AEs, (b) AEs starting within 72 hours of product administration and (c) AEs starting within 72 hours of product administration and/or considered at least possibly related to administration of study article.

Reviewer Comment on Sponsor Response to 20 December 2007 IND Information Request Letter:

The sponsor should submit analyses of (1) all AEs, (2) AEs judged by the investigator or sponsor to be at least possibly related to administration of test article (or beginning within 72 hours of the start of any administration of rescue study medication), and (3) all AEs minus those compatible with being symptoms of an

HAE attack by 4 hour time intervals (including separate and cumulative intervals in 4 hour increments, i.e, 0-4, 4-8, 0-8, 8-12, 0-12, 12-16, 0-16 hours, etc), comparing (a) subjects randomized to receive Berinert P 20 U/kg and (b) subjects randomized to placebo, with censoring of AE data as of the time they may have received rescue study medication or open-label Berinert P.

The sponsor should perform and submit these analyses for both all AEs and for all AEs that began during or within 72 hours of the start of any infusion of product. As agreed during the IND stage, all AEs reported within 72 hours of any administration of rescue study medication are to be classified as possibly related to Berinert P administration. Do not classify AEs that begin more than 72 hours following Berinert P administration but begin during or up to 72 hours of placebo rescue medication as at least possibly product related. In addition, please provide the results of pooled analyses of AEs from the initial 4 hours in the high dose randomization group combined with AEs that occur during the 4 hours following blinded administration of 20 U/kg rescue Berinert P and compare these to the incidence of AEs that occur in the placebo group during the initial 4 hours (with and without subtraction of AEs that are compatible with being due to an HAE attack). In addition, perform a similar pooled comparison of AEs without restriction as to time frame of observation, except for censoring those AEs that follow administration of rescue Berinert P (either blinded or open label). This analysis should be done with and without correction for the number of subject-hours of in-hospital observation. These analyses should also be done pooled and separately for the subgroups of AEs classified as mild, moderate, and severe in intensity.

In addition, please provide expanded definitions of the 3 numbered safety analysis populations cited in your response to this question. Given that study populations 1) and 2) both are stated to represent “all AEs” the difference between these 2 safety analysis populations is somewhat ambiguous.

The tables referenced in your response to question 7 of our 20 December 2007 letter, as contained in Attachment 2 of Module 1, volume 1 (“Module 5, Tables Q7.1 to Q7.3), state in a footnote that they include only “AEs starting during infusion and within 72 hours after end of initial [emphasis added] study drug infusion are taken into account.” Please redo these tables including AEs starting during or within 72 hours of either the initial or subsequent (e.g., study rescue medication) infusions of test article.

Sponsor’s Response to 16 April 2008 fax:

On 15 April 2008, CSLB sent CBER a fax to clarify CBER requests for additional analyses. On 6 May 2008, CSLB and CBER representatives held a conference call to address these comments. During this teleconference, CSLB stated that, for the requested analysis to pool AEs in subjects randomized to Berinert 20 U/kg and AEs occurring following administration of Berinert 20 U/kg to subjects originally randomized to receive placebo and compare to AEs following placebo, the sponsor did not wish to normalize the AE rates to person-hours of observation. CBER said that this normalization would help the test group, but if the sponsor did not want to do it, it would be optional. With regard to the additional CBER-requested safety analysis excluding HAE symptoms from AE

analyses, it was agreed that the sponsor would perform another such analysis using the protocol-defined abdominal attack HAE symptoms (nausea, vomiting, abdominal pain/cramps, and diarrhea (protocol v. 6.0, p 25). During the telecon, CSLB had informed CBER that it had not used a standard list of HAE attack symptoms in initially responding to CBER's request to exclude HAE symptoms, but had rather identified HAE attack symptoms by inspection and manual post-hoc classification.

The sponsor attempted to clarify their definitions of "four hour-safety population, after four hour-safety population without rescue study medication (C1 INH and placebo), and the after four hour-safety population with rescue study medication (C1 INH and placebo).

Reviewer Comment:

According to the sponsor's "clarifications," the AEs in each of these 3 safety populations comprises all of the AEs for the included subjects. "Deviating from the main analysis submitted with the report, all AEs not only those starting within 4 hours [four-hour safety population]/after 4 hours [after-four-hour-safety population...] after start of study drug administration entered the analysis, as the FDA required to examine a period of 72 hours after end of study drug administration." Note that, contrary to CBER's intent, the investigators, following the protocol, ascribed a causality of at least possibly related to all AEs that occurred within 72 hours of the receipt of any masked rescue study medication (whether C1-Inhibitor or placebo).

5. Item 8 from 20 Dec 2007 CBER Letter:

Please analyze and present in the BLA an intent-to-treat analysis of (a) all AEs, (b) AEs other than those compatible with HAE symptoms, and (c) AEs deemed at least possibly related to administration of study product that occur within 72 hours following the initial administration of blinded study product.

Reviewer Comment on Sponsor Response:

Please submit a list of those HAE-compatible symptoms which you removed from your analyses submitted in response to item 8(b).

In table Q8.1.4, have you included all AEs reported during or within 72 hours of the initial infusion of test article in response to item 8(c)? Throughout the BLA, whenever you state possibly related adverse events" have you included all AEs that started during or within 72 hours of any infusion of test product, regardless of whether it was blinded or given open label? Did you also include AEs that started during or within 72 hours of blinded placebo rescue medication?

For each analysis of AEs, please provide, in addition to summary statistics, a table listing the output of each analysis in terms of lists by treatment/treatment group of each AE (preferred and verbatim term) with time of onset and severity, as well as a table totaling AEs by body system and by preferred term. Please include -b(4)- code for all AE analyses (in response to all FDA queries concerning AEs) in your submission.

Sponsor's Response to 16 April 2008 fax:

CSLB expects to submit a response to this request by 16 July 2008.

Reviewer Comment:

Noted.

6. Question 9 from 20 Dec 2008 CBER Letter:

Your tables of summary statistics provided as attachments to the submission state “Final analysis as of 14Nov2007 database close) – under validation.” Please explain what validation procedures had not yet been completed with respect to the submitted tables/analyses.

Reviewer Comment on Sponsor Response:

Noted. Please indicate, as a result of programming validation, whether any results presented in the IND changed when the same data were submitted in the BLA.

Sponsor's Response to 16 April 2008 fax:

The sponsor listed ~ 2 pages of changes of results presented in the IND to those presented in the original BLA submission, including the following:

- *The number in the per protocol population changed from 41 to 42 for Berinert 20 U/kg*
- *Subjects with SAEs in the Berinert high dose group changed from 1 to 2 (5.3%).*
- *Subjects with an AE of HAE changed from 4 to 5 (3.2%) in the high dose group in the after 4 hour safety population without rescue study medication*
- *In the after 4 hour safety population with rescue study medication, the number of subjects with an AE consisting of HAE changed from 2 to 3 in the placebo plus rescue high dose Berinert group.*

Reviewer Comment:

Noted.

7. Item 13 from 20 Dec 2007 CBER Letter:

Please explain why there were 3 uses of open label Berinert P or blinded rescue medication given prior to 4 hours when throat tightness was reported for only 1 subject.

Reviewer Comment on Sponsor Response:

Please reclassify as an AE the “throat tightness” that resulted in open label study medication being administered 2 hours after subject -b(6)- had received C1-INH blinded study medication due to this AE. Please explain your logic in not originally assigning this event as an AE.

Please remove “laryngeal edema” and “throat tightness” reported for subject -b(6)- which had begun before product was administered from the list of “as treated” AEs, unless either of these AEs worsened in intensity following administration of Berinert P.

We do not understand why you state in your response to this item that subject -b(6)- “should have received open-label emergency C1-INH medication...” From your narrative description of this patient who developed a “sore throat” there appears to be no documentation that this protocol violation/early administration of blinded study rescue medication was actually an emergency. Please comment.

Sponsor’s Response to 16 April 2008 fax:

The throat tightness in subject -b(6)- will be classified as an AE. The investigator did not report throat tightness that developed 2 hours after blinded C1-INH test article as an AE because he regarded it as being part of the normal daily fluctuations of the underlying disease process.

The laryngeal edema in subject -b(6)- was listed as a non-treatment-emergent AE. No change was necessary. “Dysplasia (difficult swallowing) was documented 1.5 h after start of treatment and so is treatment emergent.”

“There is no clear documentation that the open label use for subject -b(6)- was an emergency treatment.”

Reviewer Comment:

Noted.

8. Please provide complete validation and/or qualification packages for all central laboratory non-routine clinical assays.

Sponsor’s Response to 16 April 2008 fax:

Respective validation and/or qualification packages for C1-INH activity, C1-INH antigen and C4 are located in Amendment 6.

Reviewer Comment:

See Product (CMC review memo).

PK

9. Please explain how the PK study was conducted and audited. Please provide supporting documentation to establish robustness of the data, namely, SOPs that were

followed in generating PK data, sample handling, data collection, and handling and analysis.

Sponsor's Response to 16 April 2008 fax:

CSL Behring was not involved in the conduct of the study. A quality performance report was prepared (see Attachment 2).

Reviewer Comment:

Noted. See Clinical Pharmacology review memo.

10. Please submit the details of analytical methods (both functional and antigenic) for the determination of C1 esterase inhibitor concentrations in blood or plasma.

Sponsor's Response to 16 April 2008 fax:

---b(4)----- commercial assays were used for C1-Inhibitor activity and antigen. The analyzer was a ----b(4)----- See Attachment 2.

Reviewer Comment:

Noted. See Clinical Pharmacology and CMC review memos.

11. Please note that your current analysis of PK data for functional C1INH is not acceptable. In addition, you have not submitted the PK analysis of your antigenic data. Please contact FDA's pharmacokineticist in the Division of Hematology for further information on the required PK analyses.

Sponsor's Response to 16 April 2008 fax:

Time course data fro individual antigenic data were submitted in Figures 41-80. PK analysis was performed only with the C1-INH functional assay, as the functional assay was regarded as more relevant.

CSLB has conducted a new PK analysis of CE1145_3001 using a population model confirming the PK data of CE1145_2001 or half-life and volume submitted in the BLA.

Reviewer Comment:

Noted. See Clinical Pharmacology review memo.

Immunogenicity

12. Please submit the results of anti-C1INH antibody testing for the Canadian site subjects for the pivotal trial.

Sponsor's Response to 16 April 2008 fax:

Antibodies against C1-INH were analyzed for 6 subjects from 2 Canadian centers of the pivotal trial (5F, 1M, median age 27.5 years, range 20-61 years, all Caucasian). Of these 6 subjects, 3 received placebo, of which 2 received Berinert 20 U/kg rescue medications., 2 received Berinert 10 U/kg and 1 received Berinert 20 U/kg as their randomized CTM. All subjects were to be tested for antibodies by in-house -b(4)- at week 12, but 1 of 2 Berinert 10 U/kg subjects was not tested, due to lack of material. Four of 5 subjects received Berinert either at time zero or as rescue medication and all tested negative for antibodies at week 12. One placebo subject tested negative at week 12.

Reviewer Comment:

Noted. The sponsor provided additional immunogenicity data run from stored samples from the continuation open label study. See IMMUNOGENICITY DATA section.

13. Please provide a complete assay validation package for the anti-C1INH antibody assay performed by the central laboratory.

Sponsor's Response to 16 April 2008 fax:

This is provided in Attachment 5.

Reviewer Comment:

Noted. See Product (CMC) review memo. A validation package was submitted on 29 July 2008 for the neutralizing antibody assay in amendment 14.

14. Please submit an amendment to your ongoing U.S. extension study to provide for measurement of anti-C1INH antibodies. If positive samples are obtained, it will be necessary to determine whether the antibodies are inhibitory. If positive samples are obtained, testing of baseline stored specimens may be explored to determine whether the test results were "treatment-emergent."

Sponsor's Response to 16 April 2008 fax:

CSLB will screen for the presence of antibodies using residual volume of Baseline and week 12 samples that were collected for viral screening. In case there is a positive sample at baseline, a sample from screening will also be tested. Testing for inhibitory antibodies will also be conducted using a non-validated inhibitory assay currently under development. We anticipate it will take ~ 89-010 weeks to develop and validate the assay in a best case scenario. By the end of July, either a qualification statement or a validation report will be submitted.

If a positive antibody test is obtained, the subject will be recalled for another specimen for inhibitory antibody testing.

Reviewer Comment:

Noted. The protocol amendment for antibody testing in the extension study was not submitted until November, 2008.

The following is CBER's 21 April 2008 information request fax, the sponsor's responses in italics, and my reviewer comments on those responses in bold:

1. Please provide analysis-ready dataset in -b(4)- transport files for each summary table presented for Efficacy and Safety Findings (i.e., Tables 5, 6, 7, and 8 in the Clinical Overview Section).

Sponsor Response:

CSLB expects to submit a response to this request by 30 May 2008.

Reviewer Comment: Noted. See CBER Biostatistical Review Memo.

The following are elements of CBER's 23 April 2008 information request fax, the sponsor's responses in italics, and my reviewer comments on those responses in bold:

1. Please submit a single sheet for each high dose and placebo group subject in the pivotal trial giving the subject ID (but not the randomization assignment, to permit a blinded assessment), separate graphs with severity score along the y axis for each abdominal HAE attack symptom, time from blinded study drug administration along the X axis, the response to the primary endpoint question concerning the onset of initial symptomatic relief of the HAE attack, and the numbers of (a) vomiting episodes and (b) bowel movements since the previous assessment for each assessment time point.

Sponsor's Response to 23 April 2008 fax:

CBER clarified this request during the teleconference of 6 May 2008. CSLB expected to submit the response by 16 July 2008.

Reviewer Comment:

Noted. The response was submitted in amendment 12 dated 16 July 2008.

2. You did not include a formal request for a PNR with your original BLA submission. Please refer to CBER SOPP 8801.4, Review of CBER Regulated Product Proprietary Names, Appendix 1: Request for Proprietary Name Review available at <http://www.fda.gov/cber/regsoopp/80014app1.htm>).

Sponsor's Response to 23 April 2008 fax:

The proposed trade name was undergoing internal review at the time of BLA submission. The proprietary name request was submitted 4 May 2008.

Reviewer Comment:

Noted. CBER has found the proposed proprietary name acceptable, even though it does sound like “inert!”

Three. Please submit with the BLA an analysis comparing treatment groups in terms of time from onset of the attack to time of initial relief of attack symptoms.

Sponsor reply:

CBER clarified this request during the conference call held 26 March 2008. Kaplan-Meier [sic] Curves are submitted in Attachment 7.

Reviewer Comment:

Noted. This analysis supports the sponsor’s primary endpoint analysis.

APPENDIX 5

**REVIEW OF SPONSOR AMENDMENT 7 DATED 30 May 2008
(RESPONSES TO CBER INFORMATION REQUEST FAXES TO
SPONSOR DATED 21 April, 16 MAY, AND 28 MAY 2008)**

Sponsor Responses to 21 April CBER fax and Reviewer Comments on the response.

- 1. Please provide analysis-ready dataset in -b(4)- transport files for each summary table presented for Efficacy and Safety Findings (i.e., Tables 5, 6, 7, and 8 in the Clinical Overview section.**

Sponsor Response:

A -b(4) CD-ROM containing the requested datasets is included in this submission.

Reviewer Comment:

Datasets are in the EDR submission dated 02 June 2008, the date of receipt of amendment 7.

Sponsor Responses to 16 May CBER fax and Reviewer Comments on those responses.

1. Please submit an inventory list, by subject ID numbers, of current inventory of stored serum/plasma samples on which anti-C1-INH antibody testing could be performed. Please indicate for each subject the dates the samples were drawn and the date(s) of administration of Berinert P.

Sponsor Response

The inventory was submitted in Attachment 3 of this amendment.

Reviewer Comment

The inventory lists at least 42 subjects who have residual plasma or serum from both the baseline visit and the week 12 visit of the extension study _3003. Several subjects also have residual samples from day 7-9 as well.

2. Please submit a listing of all subjects enrolled into the extension study CE145-3003, together with the number of product administration days and dates of administration of Berinert P from both the preceding study CE145-3001 and the extension study CE145-3003. Please include the subject ID numbers from both studies. The listing should contain current updated information as to the number of exposure days and the dates of exposure to Berinert P during either study, using a cutoff date in May, 2008.

Sponsor Response

The requested listing was provided with a cut-off of 7 May 2008 for extension study subjects.

Reviewer Comment

Fifty-seven subjects from the extension study are included in the list and their days of C1-INH exposure range from 1 to 55, with the vast majority of subjects having had 3 or more exposures.

3. We reiterate our recommendation that, for subjects enrolled in extension study CE145-3003 who have not come to the study site for a visit by a pre-determined date (e.g., 01 or 15 June 2008), you instruct the investigators to mail to and discuss with the subjects by telephone an updated informed consent form for obtaining additional samples for anti-C1-INH antibodies and follow-up safety chemistry, hematology and urinalysis testing, and for testing existing stored samples for anti-C1-INH antibodies. The [updated/additional] consent form should be provided with a self-addressed, stamped return envelope. Investigators should be given instructions concerning the need for prompt communication to the sponsor regarding the receipt of the signed [updated/additional] consent forms as they are received back by the investigator.

Sponsor Response

The sponsor refers to their previous responses submitted 15 May 2008. Especially to their response to CBER comment 14 on p 13 of the submission cover letter. The sponsor is presently analyzing serum samples from -3001 study subjects using an -b(4)- assay for anti-C1-INH. The firm is testing for inhibitory antibodies using a non-validated assay and continues to develop the inhibitory assay in parallel.

Reviewer Comment

Noted.

4. We also reiterate our requests to receive the additional information and analyses requested in our faxes of 16 and 23 April 2008, as discussed during our teleconference held 06 May 2008.

Sponsor Response

The sponsor refers to the firm's responses dated 15 May 2008.

Reviewer Comment

Noted.

Sponsor Response to 28 May 2008 CBER Fax

- 1. Please be advised that we are considering the possibility of presenting your data at the September BPAC and will need all relevant data requested since your BLA submission by June 13, 2008.**

Sponsor's Reply:

As stated in our 15 May 2008 response letter, we expect to submit a response to these requests by 16 July 2008.

Reviewer Comment:

Noted. CBER management elected not to take this BLA to BPAC.

APPENDIX 6

**REVIEW OF SPONSOR AMENDMENT 13 DATED 16 July 2008
(RESPONSES TO CBER INFORMATION REQUEST FAX TO
SPONSOR DATED 15 April 2008)**

The following are elements of CBER's 15 April 2008 information request fax, the sponsor's responses in italics, and my reviewer comments on those responses in bold:

4. Item 7 from 20 Dec 2007 CBER letter:

Please analyze and present in the BLA by group “as treated” the proportion of subjects reporting (a) any AEs, (b) AEs starting within 72 hours of product administration and (c) AEs starting within 72 hours of product administration and/or considered at least possibly related to administration of study article.

Reviewer Comment on Sponsor Response:

The sponsor should submit analyses of (1) all AEs, (2) AEs judged by the investigator or sponsor to be at least possibly related to administration of test article (or beginning within 72 hours of the start of any administration of rescue study medication), and (3) all AEs minus those compatible with being symptoms of an HAE attack by 4 hour time intervals (including separate and cumulative intervals in 4 hour increments, i.e, 0-4, 4-8, 0-8, 8-12, 0-12, 12-16, 0-16 hours, etc), comparing (a) subjects randomized to receive Berinert P 20 U/kg and (b) subjects randomized to placebo, with censoring of AE data as of the time they may have received rescue study medication or open-label Berinert P.

The sponsor should perform and submit these analyses for both all AEs and for all AEs that began during or within 72 hours of the start of any infusion of product. As agreed during the IND stage, all AEs reported within 72 hours of any administration of rescue study medication are to be classified as possibly related to Berinert P administration. Do not classify AEs that begin more than 72 hours following Berinert P administration but begin during or up to 72 hours of placebo rescue medication as at least possibly product related. In addition, please provide the results of pooled analyses of AEs from the initial 4 hours in the high dose randomization group combined with AEs that occur during the 4 hours following blinded administration of 20 U/kg rescue Berinert P and compare these to the incidence of AEs that occur in the placebo group during the initial 4 hours (with and without subtraction of AEs that are compatible with being due to an HAE attack). In addition, perform a similar pooled comparison of AEs without restriction as to time frame of observation, except for censoring those AEs that follow administration of rescue Berinert P (either blinded or open label). This analysis should be done with and without correction for the number of subject-hours of in-hospital observation. These analyses should also be done pooled and separately for the subgroups of AEs classified as mild, moderate, and severe in intensity.

In addition, please provide expanded definitions of the 3 numbered safety analysis populations cited in your response to this question. Given that study populations 1) and 2) both are stated to represent “all AEs” the difference between these 2 safety analysis populations is somewhat ambiguous.

The tables referenced in your response to question 7 of our 20 December 2007 letter, as contained in Attachment 2 of Module 1, volume 1 (“Module 5, Tables Q7.1 to Q7.3), state in a footnote that they include only “AEs starting during infusion and within 72 hours after end of initial [emphasis added] study drug infusion are taken into account.” Please redo these tables including AEs starting during or within 72

hours of either the initial or subsequent (e.g., study rescue medication) infusions of test article.

Sponsor's Response in Amendment 13:

The sponsor submitted a SAP, an index 9 pages long of tables, and the tables themselves in reply to this info request.

Reviewer Comment

In the ITT population analysis of all AEs in the Berinert 20 U/kg group compared to all AEs in the placebo group censored at the time of rescue study medication or open-label placebo the respective numbers of subjects with AEs was 24/43 (55.8%) and 28/42 (66.7%) for placebo. If the same analysis was restricted to at least possibly related AEs, the numbers of subjects were 8/43 (18.6%) in the Berinert 20 U/kg group and 10/42 (23.8%) in the placebo group. Serious AEs numbered 2/43 in the Berinert 20 U/kg group and zero in the placebo group. No subjects died or were discontinued due to an AE.

In the ITT population analysis through 72 hours of all AEs minus AEs manually determined by the sponsor to be compatible with HAE symptoms (HAE1) in the Berinert 20 U/kg group compared to all AEs in the placebo group censored at the time of rescue study medication or open-label placebo the respective numbers of subjects with AEs was 7 (16.7%) and 14 (2.6%), respectively. At least possibly related AEs were 2/42 (4.56%) in the placebo group and 5/43 (11.6%) in the Berinert 20 U/kg subgroup, respectively.

From Table Q4.A.8.1, In the ITT population analysis through 72 hours of all AEs minus AEs specified by the protocol to be compatible with abdominal HAE symptoms (HAE2: excluded nausea, vomiting, abdominal pain, cramps, and diarrhea) in the Berinert 20 U/kg group compared to all AEs in the placebo group censored at the time of rescue study medication or open-label placebo the respective numbers of subjects with AEs was 17/42 (40.5%) and 11/43 (25.6%), respectively. The number of SAEs was 6/42 in the placebo group and 4/43 in the Berinert 20 U/kg group.

5. Item 8 from 20 Dec 2007 CBER Letter:

Please analyze and present in the BLA an intent-to-treat analysis of (a) all AEs, (b) AEs other than those compatible with HAE symptoms, and (c) AEs deemed at least possibly related to administration of study product that occur within 72 hours following the initial administration of blinded study product.

Reviewer Comment on Sponsor Response:

Please submit a list of those HAE-compatible symptoms which you removed from your analyses submitted in response to item 8(b).

In table Q8.1.4, have you included all AEs reported during or within 72 hours of the initial infusion of test article in response to item 8(c)? Throughout the BLA, whenever you state “possibly related adverse events” have you included all AEs that started during or within 72 hours of any infusion of test product, regardless of whether it was blinded or given open label? Did you also include AEs that started during or within 72 hours of blinded placebo rescue medication?

For each analysis of AEs, please provide, in addition to summary statistics, a table listing the output of each analysis in terms of lists by treatment/treatment group of each AE (preferred and verbatim term) with time of onset and severity, as well as a table totaling AEs by body system and by preferred term. Please include -b(4)- code for all AE analyses (in response to all FDA queries concerning AEs) in your submission.

Sponsor response in Amendment 13 to item 5:

The sponsor submitted 8 tables and 1 listing in response to this information request.

Reviewer Comment

Listing Q5.B1 is a 14-page list of AEs in the ITT population that were reported to have begun during or within 72 hours after Berinert Infusion or deemed [at least] possibly related to administration of study product. A selection of notable AEs from the listing organized by different columns for each treatment group is included in the following table abstracted from the sponsor’s listing.

Selected AEs and their Time of Onset from Listing Q5.B.1 by Treatment Group, including all severe AEs meeting this listing’s criteria (up to 72 hours following Berinert randomized or Berinert Rescue or up to time of rescue study medication for placebo subjects)

| SUBJECT ID | AEs among Placebo Subjects | AEs among Berinert 10 U/kg Subjects | AEs among Berinert 20 U/kg Subjects |
|-------------------|--|--|--|
| -b(6)- | Mild throat tightness at 1.02 hrs | | |
| -b(6)- | Severe diarrhea, cramps, nausea at 0.43, 0.43, 4.18 hrs, respectively | | |
| -b(6)- | | Severe cramps | |

| | | | |
|---------------|--|---|--|
| | | sy 1.5 hrs | |
| -b(6)- | | | Severe leg cramp, severe worsening nausea, pain, headache at 0.25, 0.75, 0.75, 30 hrs |
| -b(6)- | | Severe worsening bloating, severe worsening pain at 1.5, 1.5 hrs | |
| -b(6)- | Severe headache, severe vomiting, severe nausea at 2.53, 0.6, 1.77 hr | | |
| -b(6)- | Moderate pyrexia 101.4 deg F at 28 hrs | | |
| -b(6)- | Severe worsening pain at 4.0 hrs | | |
| -b(6)- | Severe fatigue, severe nausea, moderate torso swelling at 9.78 hrs | | |
| -b(6)- | | Severe URI at 21.25 hrs | |
| -b(6)- | Severe nausea at 0.78 hrs | | |
| -b(6)- | | | Moderate anxiety at time not specified |
| -b(6)- | | | Severe URI at 53 hrs |
| -b(6)- | Severe abd pain, severe abd cramps at 1.0, 1.25 hrs | | |

| | | | |
|---------------|---|---|---|
| -b(6)- | | Severe abdominal cramps, mild finger swelling, severe nausea, mild upper lip swelling, severe exacerbation of HAE at 0.45, 0.45, 0.7, 0.87, 1.42 hrs | |
| -b(6)- | Moderate HAE abdominal exacerbation at 70 hrs | | |
| -b(6)- | | | Moderate oropharyngeal swelling at 1.75 hrs |
| -b(6)- | | | Moderate worsening abd cramps and pain at 0.75, 1.25 hrs |
| -b(6)- | Severe vomiting at 4.97 hrs | | |
| -b(6)- | Severe worsening of upper lip swelling, severe elbow swelling at 2.03 hrs and unspecified time | | |
| -b(6)- | | Severe worsening cramps and pain at 4.0 and 4.0 hrs | |
| -b(6)- | Severe worsening of facial attack at 1.75 hrs | | |

| | | | |
|---------------|---|---|--|
| -b(6)- | | | Mild BP increase at 0.75, 1.75 hrs. |
| -b(6)- | Severe dysphonia at 4.0 hrs | | |
| -b(6)- | Severe cramps, severe abdominal attack at 0.25, unspecified time | | |
| -b(6)- | | Mild worsening facial edema at 2.53 hrs. | |
| -b(6)- | | | Moderate tendonitis at unspecified time |

APPENDIX 7

REVIEW OF SPONSOR AMENDMENT 16 AND 17 DATED 3 September 2008 AND 12 September 2008 (RESPONSES TO CBER INFORMATION REQUEST FAX TO SPONSOR DATED 21 AUGUST 2008)

The following are elements of CBER's 21 August 2008 information request fax, the sponsor's responses in italics, and my reviewer comments on those responses in bold:

1. Our current thinking is that the statistical description of the efficacy outcomes of study 3001 in the draft package insert for the product should be revised to reflect the following 3 analyses (other change to the draft package insert will be requested at a later date):
 - A. Kaplan-Meier Curves for the high dose and placebo groups of the primary endpoint through 4 hours with corresponding p value for the difference in Kaplan-Meier curves. The exclusion of data beyond 4 hours avoids the artificial inflation of p values that occurs when a value of 24 hours is assigned to subjects who received rescue medication or open label CTM or analgesics or anti-emetics after 4 hours and prior to initial relief of attack symptoms. Mean and median times to initial relief of symptoms that include imputed 24 hour values and their associated p values should be deleted. Subjects receiving open label CTM or rescue medication or analgesics or anti-emetics before 4 hours and prior to initial relief of symptoms would be assigned an imputed time to initial relief of 4 hours.

- B. Kaplan-Meier Curves for the high dose and placebo groups of the primary endpoint through the last observation time point, excluding all subjects who received rescue medication or open label CTM or analgesics or anti-emetics prior to initial relief of symptoms. The p value of the difference between the curves would be provided.
- C. The proportion of subjects in each randomization treatment group that received open label CTM or rescue medication or analgesics or anti-emetics in each randomization group.

Please describe which specific data fields in which databases may be used to generate the above analyses. If derived data fields have not been provided to permit the direct calculation of the above analyses, please provide them together with a list of expanded data field definitions and the -b(4)- code for calculating the derived data fields.

Sponsor's Reply:

Analysis A – 1 (Time to start of relief censored at 4 hours)

The requested Kaplan-Meier curve will be identical to the portion of Figure 11.1.1 of the clinical study report for the primary analysis variable restricted to the [initial] 4 hour period, and will be very similar to Figure 11.2.1 of the clinical study report where we censored observations at the actual times when rescue medication was administered. The cited figures are included in Attachment 2 of the amendment.

The results of the rank tests Gehan Wilcoxon and log-rank will be similar to those of Table 11.17.3 (Statistical Appendix 16.1.9.4.1, ITT population, provided in attachment 2 to the amendment).

The sponsor does not believe that an analysis censored at 4 hours provides any new information on the efficacy.

Analysis A – 2 (Time to start of relief uncensored)

We also provide an analysis where the above times are not censored, but set to an uncensored observation of 4 hours. The p values of the Wilcoxon 2-sample test and the log-rank test will not change compared to the primary analysis in the study report. The reason that the p values in both analyses A11 and A-2 will not change is that the ranks of the times to start of relief for each subject remain the same no matter whether a 4 or 24 hour setting is chosen as the poor/failure outcome. This is because all subjects who have reported onset of relief after 4 hours received rescue medication.

It is impossible to compare the mean time to start of relief between treatment groups in an unbiased way no matter which poor/failure endpoint is chosen. This is because for subjects who received rescue medication, one would never know the real time to start of relief without rescue medication.

Analysis B

This analysis was provided in Amendment 17. The sponsor believes this analysis might be useful only as a robustness analysis, but does not believe it would be appropriate for the package insert because, in eliminating all the worst outcomes, with the proportion of worse outcomes in the placebo group, the analysis is biased to favor the placebo group. More than a quarter of the study population is excluded due to having received rescue medication prior to onset of relief of symptoms.

Analysis C

The sponsor provided a table in Amendment 17 for placebo, low dose and high dose groups that shows:

- *Proportion of subjects who received open label CTM or rescue medication or analgesics or anti-emetics (“subgroup SG with/without rescue medication” in the study report; see Table 10.5 in Attachment 4 to amendment 16)*
- *Proportion of subjects who received open label CTM open label CTM or rescue medication or analgesics or anti-emetics prior to initial relief of symptoms (not previously displayed in the study report)*
- *Proportion of subjects who received blinded study medication (additional efficacy variable in study report, see Table 11.38 in Attachment 4 of Amendment 16)*

Reviewer Comment:

Noted. Analysis A-1 should be added to the package insert (Kaplan-Meier plot and Wilcoxon test p value). The K-M curve should mirror Figure 11.1.1 but would be cut off at 4 hours. The dose response effect is evident both in Figures 11.1.1 and 11.2.1. The latter curve, which shows censoring for open label emergency Berinert, rescue CTM, analgesics, or anti-emetics given prior to time of initial relief of HAE attack symptoms, shows that 3 subjects in the placebo group received one of the above prohibited medications between 1 and 4 hours. In addition, 1 subject received confounding medication at time zero. Although Figure 11.2.1 states for Berinert 20 U/kg bw “N-43, censored – 5),” Figure 11.1.1 shows that 6 subjects in this high dose group were assigned [an imputed time] to initial relief of symptoms of 24 hours. The sponsor should explain this discrepancy. The 2-sided p value for the Generalized Wilcoxon test for Berinert high dose vs. placebo using TTREL with censoring at the time of study rescue medication, analgesics, or anti-emetics is 0.005, according to the sponsor’s analysis. In this analysis, a total of 22 subjects were censored, according to the sponsor’s analysis.

I agree with the sponsor that important information regarding efficacy is lost by removing subjects who received rescue medication prior to onset of relief of symptoms, and that, because the use of rescue medication was nearly 3 times more common in the placebo group than in the high dose group, the removal of data for these subjects does bias the analysis in favor of the placebo. I agree that this analysis would not be contributory for the package insert.

Regarding analysis C, while the sponsor's 3rd bullet in their reply was the *a priori* analysis, I believe that analyses 1 and 2 are more informative. I recommend the results of analysis in the first bullet of the sponsor's reply be presented in the package insert. The sponsor cites Table 10.5 as supportive to the first bullet requested analysis. This table shows a total of only 4 subjects across the 3 randomization groups who received analgesics/anti-emetics/C1-Inhibitor as concomitant medications (. This total would seem to conflict with the revised information on the use of concomitant medications presented in the safety update, which strongly suggests that the actual number was much larger than this. [See section dealing with review of the safety update]

2. Whereas the original BLA contained 34 datasets, the 103 page list of variable definitions from your 02 May 2008 submission appears to only list the variable names for 10 datasets. For example, the expanded definitions for all of the data fields in original BLA databases ADCM and ADEFF do not appear to have been included. Please provide a complete list of expanded variable definitions for each dataset included in the original BLA submission as well as for any additional datasets you may submit in the future at the time they are submitted.

Sponsor's Reply:

Rather than provide the requested information, the sponsor describes the location of the original datasets and the documents supporting the sponsor's responses to the 20 December 2007 FDA information request (made prior to BLA submission based on information submitted to the IND).

Reviewer Comment:

Despite repeated requests, the sponsor's narrative response still has not addressed our repeated requests to provide expanded definitions for all of the data fields in each of the data sets included in the original submission! During the teleconference held on 31 October 2008 between Drs. D'Agnello and Farshid of this Division, Ms. Cagungun, CSLB, and myself, I indicated to the sponsor that some of the sponsor's recent BLA Amendment responses to our [21 August] information request regarding statistics and databases appeared to be incomplete and may indicate that the sponsor misunderstood some of the questions we were asking. I encouraged Mr. Hartman to re-read our questions and their replies.

3. We note that your 02 May 2008 submission lists 10 analysis datasets ("CE1145_3001 – List of datasets – Additional analysis referring to Dec 20, 2007 fax from FDA"), yet the submission appears to contain only 2 of these datasets (ADEFFDA3.xpt and ADEFDA3B.xpt). Please identify the location of the remaining 8 datasets.

Sponsor's Reply:

“During preparation of the 02 May 2008 submission, the missing 8 files were inadvertently not included in the submission” They are included in a CD ROM in Attachment 5 of Amendment 16.

Reviewer Comment:

Noted.

4. Please identify the variable name for the derived data field for the difference between the time randomized CTM is administered and the start date and time of concomitant analgesics and anti-emetics. Please identify in the submission the location of the -b(4)- code used to calculate this derived data field.

Sponsor's Reply:

Variable TONALG represents “Time of start of analgesics/anti-emetics/C1-INH/FFP concomitant medication.” This datetime variable captures date and time of start in one variable.

In concomitant medication dataset ADCM, TONALG is filled with the start date of the medication if the medication is in the list of analgesics/anti-emetics/C1-INH/FFP [FFP contains C1-INH].

“In all [databases other than ADCM, TONALG]... contains the first start date of an analgesics/anti-emetics/...concomitant medication within a subject.

TONALG is derived in programs DSUBGRP.-b(4)- and DADCMSEL.-b(4)-. Program DADCMSEL.-b(4)- flags concomitant medications if they are prohibited during the study.

DSUBGRP.-b(4)- generates general variables needed for analysis. These general variables are merged to all data sets within the study.

Variable TTANA represents “Time to between start of randomized CTM to start of analgesics/anti-emetics/C1-INH/FFP concomitant medication in hours.

“TTANA = TONALG minus start date/time of study drug administration (RFSTDI and FFSTDI)”

TTANA is derived in the program DSUBGRP.-b(4)-

Reviewer Comment:

It is inherently confusing for the sponsor to have populated the field, TONALG differently, depending on the database!

5. Please identify the variable name for the derived data field for the difference between the time randomized CTM is administered and the start data and time of open label CTM or blinded rescue medication. Please identify in the submission the location of the -b(4)- code used to calculate this derived data field.

Sponsor's Reply:

Variable TTRESC represents "Time between start of randomized CTM and start of rescue medication.

There is currently no derived variable for the difference between the time randomized CTM is administered and the start time of emergency mediation. However, differences can be calculated using the general variables below, which are part of every dataset:

RFSTDI = Start Date of study drug administration

RFSTTI = Start time of study drug administration.

RESCSTDI = Start date of rescue study drug administration

RESCSTDI = Start time of rescue study drug administration

EMSTDI = Start date of emergency study drug administration

EMSTTI = Start time of emergency study drug administration

Reviewer Comment:

Noted.

6. Please define the variable name and values for CENS, TTREL, TTRELCEN, RECSTDI, and TRIELP.

Sponsor's Reply:

Descriptions of all variables can be found in the DEFINE.PDF document located in the folder STATISTICAL/3001/PROGRAMS.

CENS = TtRelResC – Censored Obs. CENS = 1 if time to relief from rescue medication (TTRELRSC) was censored; otherwise CENS = 0

TTREL = "Time of start of relieve [sic] of symptoms (TOSREL) – Start of first study drug administration (RFSTDI, RFSTTI)" (DEFINE PDF, PP 85, 111).

TTRELCEN = TtRel censored with time to rescue med. TTRELCEN = Time to start of relief of symptoms (TTREL) if time of relief [was] before rescue medication or no rescue medication was given. TTRELCEN = Start rescue medication (RESCSTDI, RESCSTTI) minus Start study drug administration

(RFSTDI, RFSTTI) if any rescue medication given before onset of relief.
(DEFINE.PDF p 99)

RESCSTDI = Start date of rescue medication. “Please note: In datasets ADCM, ADSUB, ADVS, and ADVSI variable RESCSTDI has the label ‘Start Date of treatment (-b(4)- date)’ which is not correct. The correct label should have been “Start date of rescue medication.” The same error applies to RESCSTTI.

Reviewer Comment:

Corrections to sponsor’s original labeling of field names noted.

7. Please identify which databases and variables were used to calculate the Kaplan-Meier curves for the primary endpoint presented in the study report.

Sponsor’s Reply:

TTRELP from the dataset ADEFF was used to create Figures 11.1.1 – 11.1.3 “Primary efficacy variable: TtRel+: Time between start of study medication administration and start of relief of symptoms from HAE – non-responders set to 24 hours.” TRTAN was used for discriminating between treatment groups.

Reviewer Comment:

The results of the sponsor’s primary endpoint analysis using TTRELP is shown in table 11.17.1 which indicates that in the ITT population the 1-sided p value for the 2-sample Wilcoxon test between high dose 20 U/kg Berinert C1-Inhibitor and placebo groups was 0.0025 (2-sided p value of 0.005). The 2-sided log rank test gave a value of p = 0.008 in the sponsor’s hands. Dr. Wang of CBER DBE obtained the same result in an analysis using TTRELP using 44 Berinert high dose subjects compared to the sponsor’s analysis which used 43.

Amendment 17 contains a “Guide to datasets and programs for additional analysis required by FDA fax dated 21 August 2008” and various PDF documents containing tables and statistical results for analyses different from what FDA had requested in its 21 August 2008 fax; No PDF tables included in the submission appear to correspond to analysis 1A of FDA’s 21 August 2008 fax. All but one of the provided analyses were not requested by FDA; these analyses do not distinguish as to whether prohibited medications or rescue medication were given prior to or after time to initial relief of symptoms had been received, plus a TOC of the PDFs. During a teleconference at the IND stage, FDA informed the sponsor that we did not believe analyses of time to initial relief of HAE attack symptoms that impute or censor subjects based on use of prohibited or rescue medication after a primary endpoint event had already occurred were useful. FDA did say, however, that the sponsor could provide one such analysis as a purely exploratory analysis.

Although the cover letter to Amendment 17 dated 12 September 2008 states “The purpose of this submission is to supply a complete response to

item 1, no such response is provided, either in the form of a narrative discussion or tables or figures responding to FDA item 1A request.

The missing item 1A analysis from Amendment 17 read as follows:

Kaplan-Meier Curves for the high dose and placebo groups of the primary endpoint through 4 hours with corresponding p value for the difference in Kaplan-Meier curves. The exclusion of data beyond 4 hours avoids the artificial inflation of p values that occurs when a value of 24 hours is assigned to subjects who received rescue medication or open label CTM or analgesics or anti-emetics after 4 hours and prior to initial relief of attack symptoms. Mean and median times to initial relief of symptoms that include imputed 24 hour values and their associated p values should be deleted. **Subjects receiving open label CTM or rescue medication or analgesics or anti-emetics before 4 hours and prior to initial relief of symptoms would be assigned an imputed time to initial relief of 4 hours [emphasis added.]**

Appendix 8 – Subgroup Analyses of Impact I study by Age and Sex

The median time to initial relief of symptoms among men (n = 14) in the placebo group was more than double that of women (n = 28) (3.02 vs. 1.33 hrs, see Table 25 study report p 94). This was also seen in the Berinert 10 U/kg group. However, the opposite was observed in the Berinert 20 U/kg group, where the median TTRELP for men (n = 13) was 0.483 hrs compared to 0.733 hrs for women (n = 30).

Analysis of primary endpoint, TTRELP, (median) by age ranges in study CE1145_3001

| Age Range | Placebo TTRELP /N | Berinert 10 U/kg TTRELP / N | Berinert 20 U/k TTRELP / N |
|---------------|-------------------|-----------------------------|----------------------------|
| 3 – 11 yrs | 0.667 / 2 | - | 0.25 / 1 |
| 12 – 16 yrs | 0.467 / 3 | 0.686 / 3 | 0.333 / 4 |
| > 16 – 64 yrs | 3.000 / 37 | 1.350 / 35 | 0.683 / 35 |
| > 65 yrs | - | 0.167 / 1 | 0.483 / 3 |

The numbers of children and geriatric patients > 65 years were too small to draw conclusions. Nevertheless, in children, adolescents, and adults, the median TTRELP in either Berinert Group was less than in the corresponding placebo subgroup.

There were too few blacks and “other” races to have a meaningful analysis of efficacy by race.

HFM- 392

CBER/OBRR/DH/CRB