



Our STN: BL 125287/0

CSL Behring GmbH
Attention: Paul Hartmann, R.Ph.
1020 First Avenue
King of Prussia, PA 19406-0901

Dear Mr. Hartmann:

We have completed the review of all submissions to your biologics license application (BLA) for C1 Esterase Inhibitor (Human) (C-INH) for the treatment of acute attacks of hereditary angioedema (HAE), submitted under section 351 of the Public Health Service Act, except as noted below.

We acknowledge receipt of your amendments dated October 30 2008 and December 1, 2008. You may cross reference applicable sections of the amendments in your complete response to this letter and we will review those sections as a part of your complete response.

In our review, we find that the information and data submitted are inadequate for final approval action based on the deficiencies outlined below.

Chemistry, Manufacturing, and Controls (CMC)

1. Outstanding inspectional issues from the pre-licensing inspection conducted on May 26 to June 3, 2008, have yet to be resolved.
2. Please note that your current viral inactivation and removal steps do not provide a sufficient margin of safety with regard to HIV and PRV. Because of the unusual results obtained for HIV and PRV in the pasteurization step and the limitations of hydrophobic interaction chromatography (HIC) step, an additional robust and effective viral clearance step, ---b(4)-----, should be included in the manufacturing process of Berinert P to enhance its viral clearance capacity for both enveloped and non-enveloped viruses, and to provide more assurance with regard to viral safety of the product.

Specifically, in your manufacturing process, pasteurization is the only dedicated viral clearance step. This step is expected to be robust and effective against enveloped viruses. However, your viral validation data point to unexpected heat stability of HIV and PRV in the pasteurization step under the manufacturing conditions for Berinert P. As demonstrated in your viral clearance studies, HIV was inactivated later in the process (up to --b(4)--), indicating heat stability of the virus in Berinert P --b(4)---. This heat

inactivation pattern for HIV has not been reported for other products (including all other CSL products). You have noted that the stabilizing conditions for HIV are unknown and speculated that the C1-INH molecule itself may have HIV-stabilizing impact. Furthermore your data indicate that the stabilizing conditions appear to be different depending on the production lots. This further underscores unexpected behavior of pasteurization step and its lack of robustness under the conditions in which your product is manufactured. Similarly, as your experimental data demonstrated, PRV is stabilized to a very high degree against heat inactivation under your production conditions, resulting in PRV inactivation being achieved only after -b(4)---- with residual virus remaining. The other validated virus clearance step in your manufacturing process is HIC, which contributes to virus clearance, but is inherently less reliable. Therefore, because of unexpected heat stability of HIV and PRV in the pasteurization step and the limitations of HIC, an additional robust and effective viral clearance step should be included in the manufacturing process of Berinert P to enhance its viral clearance capacity for both enveloped and non-enveloped viruses.

3. Please provide stability data based on the modified stability protocol that includes the additional stability indicating tests; -----b(4)-----

4. Validation packages for the determination of active C1INH in human serum and for anti-C1INH antibody assay (Amendment 6, Attachments 5 and 6, respectively) show that in both assays the linearity was established over --b(4)------. Please use a minimum of five concentrations to demonstrate linearity of these assays (ICH Guideline Q2B (1996) for Validation of analytical procedures). If another approach was used, please provide justification.

CLINICAL

5. 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. For example:
 - The protocol indicates that subjects who received analgesics or anti-emetics prior to reporting their 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” and “time of start of analgesics/anti-emetics/C1 INH/FFP”) 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.

- We understand from our telephone conversation held on November 12, 2008 with representatives of your firm and --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.”

Therefore, we request you submit:

- a 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. These are needed to resolve possible/apparent discrepancies between the original CRF entries and investigators’ responses to the data query forms.
 - table and database showing the dates and 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.” The times of administration of “any rescue medication” should reflect the actual hospital source

medication records for all instances where these medications were indicated as “continuing” or “being continued” on the original CRFs.

- We request you re-analyze the study primary endpoint, taking into account “any rescue medication,” including both narcotic and 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.
- 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 database. However, as noted above, the original ADCM database has missing values for variable “TONALG” (“Date/Time of first analgesic after start of first administration in the respective time window”) 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 November 12, 2008 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, “tranexamic” [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.

Additional details and problems concerning your data and submissions that have impeded our validation of your efficacy analyses are listed in the Appendix to this letter.

6. 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.
7. Please indicate the date the blind was broken for phase II/III study CE1145_3001 (IMPACT I).

8. 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.
9. Please provide a table and 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.)
10. When you redo and resubmit your analyses of the primary endpoint, please use the actual times of administration of “any rescue 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. This would be consistent with the feature of the protocol which specified to count as treatment failures subjects with missing data for time to initial relief of symptoms.
11. 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.
12. 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 include all:
 - a) 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) such medications administered from 5 hours prior to ToS through time to complete relief of symptoms.

13. In amendment 16 submitted September 3, 2008 in response to our August 21, 2008 information request item 1C, you cited Table 10.5 in support 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 conflicts with the revised information on the use of concomitant medications presented in the safety update.

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 date 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 should 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).

14. 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.

15. We note that in the concomitant medication original database ADCM, 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.
16. 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.” 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.” 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.
17. Subject -b(6)- experienced a severe AE recorded as an exacerbation of hereditary angioedema. This subject received rescue medication on March 20, 2006 at “61500,” according to column “RESCSTTI” in the ADAEFDA database. Please explain what is meant by “61500”.
18. Please provide additional immunogenicity data from a total of at least 40 HAE subjects who have received multiple exposures of the product. 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, over a period of up to 12 months. Subjects with antibodies positive by -b(4)- should be tested for inhibitory antibodies using a validated assay. When submitting the data please describe in detail attempts to correlate treatment-emergent antibodies with AEs.

19. Please submit data from at least 40 subjects for routine chemistry, including renal and liver function and aminotransferases, hematology, and urinalysis, including microscopic examination of urine sediment, from following single and multiple dose exposure to the product and compare these to baseline values.

LABELING

20. We reserve comment on the proposed labeling until the application is otherwise acceptable.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products February, 2000 (<http://www.fda.gov/cber/gdlns/mtpdufa.pdf>). For Non PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants (<http://www.fda.gov/cber/regsopp/81011.htm>).

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application).

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

If you have any questions, please contact the Regulatory Project Manager, Nannette Cagungun at (301) 827-6174.

Sincerely yours,

Basil Golding, M.D.
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research

APPENDIX

- 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 TTRELP (TTREL+) for these subjects.
- 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” for this variable. Please explain this discrepancy.
- 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, phenegan, and odanasetron, among others. Please comment.
- In partial response (September 3, 2008) to question 1A of our information request fax dated August 21, 2008, you state “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.
- 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 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 after 4 hours **but before start of relief**) – ITT population [emphasis added].” Please clarify.

- In addition, item 1 of our August 21, 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 September 3, 2008, and in Amendment 17 dated September 12, 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. Please clarify.

- 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.
- In amendment 16 you state on p 6 in partial response to our request 4 of our August 21, 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.
- In Amendment 17 submitted September 12, 2008, p 2 of “Guide to datasets and programs for additional analysis required by FDA fax dated 21August,2008,” it states that:
 - “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.”
 - “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. Please supply this document.

- We note that the variable “SGANAN” (SG [subgroup] with/without analgesics/anti-emeticum”) 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: Antihistamines [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 in 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)
- 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.
- 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).

- 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 August 21, 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 November 12, 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, Status October26, 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 (time of start of study treatment) until $TOSREL$ (the time of start of relief of symptoms). Please redo and resubmit your primary endpoint analyses accordingly.