

MEDICAL REVIEW OF SPONSOR'S COMPLETE RESPONSE TO CR
LETTER – Preliminary Review – 1st Info Request Items

STN 125287/0/25

BERINERT P

DATE RECEIVED BY FDA: 10 April 2009

1. We reiterate our request #6 from our Complete Review letter to you to “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.” Your amendment 25 states that either 2 or 4 databases must be used to reproduce the primary endpoint analyses. Please ensure in the to-be-submitted database that all variables have a single consistent definition. We note that in your previously submitted databases, some variables’ definitions vary according to the database in which they are found.
2. You state under the 2nd bullet on p 10 of 14 in your “Reviewer Guide to the Database” submitted with amendment 25, “If the subject was asleep at a certain point and confirmed symptom relief after awakening (variable EFIMPROV), the time point of symptom relief onset was defined as the first time of the last period of sleep before symptom relief.” Please clarify the meaning of this statement.
3. On p 8 of 14 of the “Reviewer Guide to the Database” submitted with amendment 25, you state:

In case prohibited/discouraged concomitant medication according to the respective list...*PROHMED.xpt* [i.e., the list for the additional robustness analysis conducted to address CBER’s *Comment 5C*]) was administered over a period of time starting before ToS and ending after ToS (before or after ToSRel), TtRel+ was not imputed with the poor/failure outcome of 24 hours if there was an investigator comment confirming that the medication was not administered during the following time periods:

- between ToS and TtRel [sic?] for the original analysis

- between 5 hours before ToS to ToSRel for non-narcotic pain medication and ToS to ToSRel for all other medications in the list for the **additional robustness analysis (PROHMED.xpt)**.

This appears to conflict with the statement on p 13 of 14 of this document which states:

For the additional robustness analysis conducted in response to CBER's Comment 5C, the following additional derivation criteria need to be taken into account to complete step 2 (additional variables DATACOM, EXCLTEXT, EXCLRES, HAEDIFF, HAEDIFFH):

- The extended time window for prohibited medication use, i.e., from 5 hours before start of study medication to onset of symptom relief.
- Administration of any of the prohibited concomitant medications on the list for the additional robustness analysis ((PROHMED.xpt) in this extended time window.

Please clarify which of the above statements is correct. If the former is correct, please redo and resubmit the primary endpoint robustness analysis that uses the extended time window of from 5 hours prior to administration of blinded study medication until ToSRel, as requested in our CR letter.

Please also clarify how and why the variables, HAEDIFF and HAEDIFFH [variables containing the time between the estimated start of attack under study and the event in EVENT] were used for step 2 of the "robustness" analysis submitted in amendment 25 in response to the CR letter.

4. Please clarify what values were imputed for variables HELPE AND HELLPTI in instances where CRF values for both CMONGO and CMENDTF were missing.
5. You state in part in response to our CR letter item 5D that narcotic pain medications only resulted in imputation of a poor/failure outcome of the primary endpoint "If they were administered in the critical time period between start of randomized study medication and

- start of symptom relief, or 24 hours after start of randomized study medication.” Please clarify when a poor/failure was imputed if these medications were administered “between start of randomized study medication and start of symptom relief” vs. if they were administered between start of randomized study medication and 24 hours.
6. You state in response to CBER CR letter item 14 that subject -b(6)-, who was randomized to the Berinert 20 U/kg group, received open-label emergency study medication at 1.09 hours after the start of randomized, blinded study medication. This conflicts with your statement in response to CBER CR letter item 11 that each of the 11 subjects in the study who received C1-INH as open-label concomitant medication had documented start dates for concomitant open-label C1-INH that were “At least 2.5 days after administration of randomized study medication, and “Always after time of start of relief.” Further, in your response to item 11, subject -b(6)- is not listed among the 11 subjects who received C1-INH as open-label concomitant medication. Please clarify.
 7. By our count, a total of 55 subjects are listed in your QRL_Q6C database submitted with amendment 25 in which you indicated in the field named RIMPUTE that you have imputed the value for the primary endpoint, time to initial relief of symptoms. Yet, in the primary endpoint field named RTTREL, only 4 subjects have an imputed value of 24 hours. The remaining 51 subjects for whom you indicated you have imputed a primary endpoint “failure” value have a dot as the field entry. Please clarify. We note the 4 subjects with a 24 hour imputed value for RTTREL have missing data for time of initial relief variable, ToSRel. The remaining 51 subjects have values in the RIMPREAS (Reason for imputation (robust)) field corresponding to “Prohibited med. Given before time to onset of relief” or “Blinded rescue med. Given before time to onset of relief.”
 8. You state in response to CBER CR letter item 10 that “Hospital records/source data to confirm the actual times of administration were collected from all subjects who, between 5 hours before and 24 hours after start of randomized study medication, received any of the concomitant medications included in the list *PROHMED.xpt* for the additional robustness analysis.” We understand this list to include "any rescue medication" (including all "discouraged" (narcotic and non-narcotic analgesics and antiemetics) and all 6 classes of "Non-permitted" medications) being taken prior to study start and where such medication was recorded as “ongoing” or for which the stop date

- was missing. In cases where the investigator's response to your query concerning whether such medications were taken during the critical part of the study conflicts with the hospital medication record, it was our intent that you use the latter data rather than the investigators' responses to your query sheets to construct your revised databases and analyses. Please revise your databases and analyses submitted in your complete response to our CR letter accordingly if you did use the hospital medication records in cases where they conflicted with the investigators' responses to your query sheets.
9. Please submit a revised draft package insert at this time that takes into account the edits sent to you in 2008. The CLINICAL STUDIES section should provide a Kaplan-Meier curve for the robustness analysis based on imputation of a > 4 hour value for any subject who took any of the "discouraged" or "forbidden" medications (including non-narcotic analgesics) anytime between 5 hours prior to ToS and ToSRel. You may also include (below the results of the above analysis) the results of the same analysis, except that > 4 hour values are not imputed solely because a subject was documented to have received a non-narcotic pain medication between 5 hours prior to ToS and ToSRel. Please submit the results and methodology for the latter analysis, which we shall designate as the "R2 analysis."
 10. Please reference the specific amendment in which you explain in narrative fashion as well as using -b(4)-- code, exactly how you calculated the primary endpoint. Your response to the CR letter does not provide this information in a stand alone statement, but rather references the original BLA submission and amendments without being specific as to location. Please submit a flow diagram, similar to the one on p 14 of 14 of the "REVIEWER GUIDE TO THE DATABASE," that details the methodology used to perform the "robustness" and "R2" analyses.
 11. Please redo and resubmit database QRL_Q6C with corresponding fieldnames from the robustness and R2 analyses side by side.

CBER's CR Letter Clinical Items followed by Sponsor's Responses (in italics) and Reviewer Comments (in bold)

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 SAS 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.

Sponsor’s Response

CSLB Response 5A:

Introduction – Study Conduct and Analysis According to Protocol

When conducting the primary endpoint analyses of the study, CSLB strictly adhered to the study protocol and the Statistical Analysis Plan (SAP) that was prepared and signed off well prior to initiating any data analyses, as detailed in the following subsections:

CSLB’s Interpretation/Understanding of the Term “Pain Medication”

Please refer to the Cover Letter (in CDROM subfolder 1_Cover Letter + Attachments A, B, C) that contains CSLB’s and outside consultants’ positions concerning the use of non-narcotic pain medications for the treatment of acute HAE attacks.

Because non-narcotic pain medications are regarded as ineffective for the treatment of acute HAE attacks, CSLB restricted the term “pain medication” to denote narcotic pain medications in the study protocol and the SAP.

To verify and track the use of prohibited medication, a prohibited medication list was prepared and updated with the new medications that were administered in the course of study conduct. This list consequently only contained narcotic pain medications. The same list was included in the SAPs for the interim and final analyses (see CDROM subfolder Attachment 8 for SAPs) to perform the imputation of a poor/failure outcome of 24 hours if any of the specified prohibited medications was given in the critical time

window for efficacy assessment. The prohibited medication list in Appendix IVa of the SAP for the final analysis, Version 2.0 dated 26 October 2007, was the basis for the original analyses of the primary endpoint. Therefore, the use of non-narcotic pain medication administration was not defined as an exclusion criterion and not taken into account for the primary endpoint analyses, unlike the use of prohibited narcotic pain medications that resulted in the imputation of a poor/failure outcome.

In order to clarify the reasons for the missing values pointed out in *CBER Comment 5A*, the variables in the concomitant medications dataset ADCM (original database of safety follow-up; location: CDROM subfolder *3_Datasets and Programs\3.2_Original database safety follow-up*; additionally located in CDROM subfolder *Attachment 5A*) are explained below:

(1) Data recorded by the investigator on the case report form (CRF):

For each concomitant medication, the investigator was to document the following items on the “Prior/concomitant medication” CRF with respect to timing of administration:

- “Check if drug started prior to study” (variable ZPRIOR);
- Start date (variable CMSTDTF) and start time (variable CMSTTMF);
- “Check if ongoing” (variable CMONGO);
- End date (variable CMENDTF).

(2) Investigator comments:

The concomitant medications dataset ADCM also includes the investigator comments (variable INVCMT) confirming that prohibited concomitant medications (i.e., according to Appendix IVa of final SAP, Version 2.0) documented as “prior” and “ongoing” on the Prior/concomitant medication CRF were not administered in the queried, critical time period. This means that the variable INVCMT only contains a value if the investigator confirmed (in response to a query) that the prohibited concomitant medication was not administered during the queried, critical time period. For details on CSLB’s queries sent to investigators and the investigators’ responses, please refer to CSLB Response 5B1+5B2.

(c) The variable TOANALG in dataset ADCM represents the start date (HELPS) and time (HELPTI) of administration of prohibited medications and was only derived under the following conditions:

- *For analgesics, anti-emetics, open-label C1-INH or fresh frozen plasma (FFP), as listed in Appendix IVa of the SAP for the final analysis, Version 2.0 (located in CDROM subfolder Attachment 8);*
- *If the aforementioned prohibited medications were administered between start of study medication (ToS) and 24 hours thereafter.*

As a consequence, TOANALG is missing in all other cases. In particular, TOANALG was not derived:

- *For non-narcotic pain medications (such as aspirin, etc) that were not part of the prohibited medication list in SAP, Version 2.0, Appendix IVa. Please refer to the Cover Letter (located in CDROM subfolder 1_Cover Letter + Attachments A, B, C) that provides CSLB's and outside consultants' positions concerning the ineffectiveness of non-narcotic analgesics in the treatment of acute HAE attacks.*
- *For medications given only prior to start of study medication, i.e., with an end date (HELPE) prior to start of study medication.*
- *If the investigator comment (variable INVCMT) confirmed that the prohibited medication in question was not used between start of study medication and start of symptom relief.*

In the datasets other than ADCM that use TOANALG on a subject level, the earliest TOANALG (i.e., minimum TOANALG) was taken into account for this subject for calculation of the primary endpoint, time to start of symptom relief (TtRel+). See the Reviewer Guide to the Database for the two different definitions of TtRel+ used in the original analysis and the additional robustness analysis conducted to address CBER Comment 5C (location: CDROM subfolder 3_Datasets and Programs\3.1_Reviewer Guide to Database).

(4) Impact of prohibited concomitant medications on the primary endpoint TtRel+:

One of the pre-specified reasons to set the primary endpoint TtRel+ to a poor/failure outcome of 24 hours was the administration of narcotic analgesics, anti-emetics, open-label C1-INH or FFP between ToS and ToSRel. If TOANALG contains a value (based on the criteria described in point 3c) on the previous page) and if TOANALG occurred before ToSRel, then TtRel+ was set to a poor/failure outcome of 24 hours.

Of note, the variable TOANALG does not reflect any of the other reasons for setting TtRel+ to a poor/failure outcome (i.e., administration of rescue study medication or missing ToSRel value).

Reviewer Comment

As documented in the sponsor's response to CR item __, the sponsor never submitted version 2.0 of the SAP, i.e., the version the sponsor used in their original BLA submission analyses, to the IND. Because the sponsor did not document at the time the SAP version 2.0 was written reasons certain forbidden medications and pain reliever medications were to result in imputation of a "poor/failure" 24 hour value for the primary endpoint variable, time to initial relief of symptoms (TTRELP), I do not consider primary endpoint analyses following SAP version 2.0 to be valid. The FDA review will focus on the re-analysis of the primary endpoint requested in the CR letter, which imputes a (> 4 hour or) 24 hour value for the primary endpoint for subjects who were documented to have taken "any rescue medication," meaning any of the "forbidden" medications listed in the protocol, or any (narcotic or non-narcotic) analgesic or anti-emetic any time in the time window from 5 hours prior to the start of study test medication to time to initial relief of symptoms. The sponsor calls this analysis the "robustness" analysis and has created various robustness analysis datasets for this analysis.

The 3 consultants' letters indicate the authors are unaware of any published information that bear on whether non-narcotic analgesics, including ASA, NSAIDs, and acetaminophen, may affect the intensity of any abdominal HAE symptoms. The physician consultants' letters do not address the question, raised by FDA in the CR letter, as to whether any facial HAE attack symptoms, such as facial tightness, might be affected by non-narcotic analgesics. The head of the HAE patient organization states in his letter he is unaware of any HAE patient who has ever discussed with his/her physician whether non-narcotic analgesics may affect the intensity of HAE symptoms. Note that whether non-narcotic analgesics are capable of causing complete relief from HAE attack symptoms is not at issue. Rather, because the primary endpoint relates to initial (i.e., partial) relief of symptoms, what is at issue is whether non-narcotic may moderate the intensity of any type of abdominal or facial HAE attack symptom, even to a mild, but perceptible degree. In the absence of controlled clinical data to resolve this question, the FDA analysis of the primary endpoint will emphasize imputation of a "poor/failure" value of > 4 hours or 24 hours for subjects who were documented to have taken any narcotic or non-narcotic pain reliever, anti-emetic, or forbidden medication ("any rescue medication") in the pertinent time window. The labeling may also show the result of an

analysis that excludes non-narcotic analgesics from such “poor/failure” imputations, as a robustness analysis (which I shall call the R2 analysis).

The sponsor’s statement, “Because non-narcotic pain medications are regarded as ineffective for the treatment of acute HAE attacks, CSLB restricted the term “pain medication” to denote *narcotic* pain medications in the study protocol...” is inaccurate:

The protocol stated on p 21 under the heading “Pain medication and anti-emetics”

“Due to potential interference with assessment of the primary efficacy variable, the use of pain medication (*meaning narcotic 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.”

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]

It is correct that use of narcotic analgesics, rather than all analgesics, taken between start of attack and administration of study treatment, was a protocol exclusion criterion. However, the definition of the primary endpoint used the terms analgesics and pain medication with restricting these to narcotic analgesics. While the sponsor asserts they meant narcotic analgesics, the sponsor has not offered any convincing evidence to know that was the case at the time the protocol was written.

The sponsor’s use of the derived variable, $TOANALG$ in the original BLA submission and in the re-analysis submitted in response to the CR letter using the original analysis method is judged to not be sufficiently conservative because

(1) it does not use the complete list of forbidden medications listed in the protocol (use of epsilon amino caproic acid, tranexamic acid, and products (other than FFP and C1-INH) which share a mechanism of action with C1-Esterase Inhibitor,

(2) it does not take into account non-narcotic analgesics, and

(3) it records a value only if narcotic analgesics, anti-emetics, open-label C1-INH or FFP were between ToS and ToSRel. If “any rescue medication” were taken shortly before ToS they could confound interpretation of the study endpoints. For this reason, FDA established in the CR letter a relevant timeframe for the re-analysis of the primary endpoint of “any rescue medication” being taken anytime from 5 hours prior to ToS to ToSRel (for the primary endpoint) or from 5 hours prior to ToS to time to complete relief of symptoms for the latter study variable.

- 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.**

Sponsor’s Response

CSLB Response 5B1+5B2:

*Listing_Q5b12 and -b(4)- dataset CRLQ5b12 in CDRom subfolder Attachment 5B1+5B2 present the requested data **for subjects who received “non-permitted” medications** starting prior to start of blinded study medication and recorded by the investigator as “ongoing” on the prior/concomitant medication CRF. **In response to CSLB’s queries, stop dates were obtained for Subjects ---b(6)-----, and these are reflected in the listing and dataset.***

*These **queried “non-permitted” medications** include only the medications on the prohibited medication list in Appendix IVa of the SAP for the final analysis (Version 2.0 dated 26 October 2007), and they **do not comprise the additional “discouraged” medications from CBER’s list of 13 November 2008, as no queries were sent with respect to these medications.** However, CSLB has generated the requested dataset CRL_Q6BR to include the*

additional medications from CBER's list (see CSLB Response 6 and CDROM subfolder Attachment 6\revised data robustness analysis).

Thus, queries were only sent for subjects who were documented on the prior/concomitant medication CRF to have received any of the following:

- *Narcotic pain medication, and/or*
- *Anti-emetics, and/or*
- *Open-label C1-INH, and/or*
- *FFP*

*starting before the start of the attack/start of study medication and documented as "ongoing" (CMONGO = "ongoing") on the prior/concomitant medication CRF. **Copies of the individual Data Clarification Forms (DCF's) are located in CDROM subfolder Attachment 5B1+5B2.***

*The **investigator's responses to CSLB's queries** were entered into the clinical database system (Oracle Clinical) and are available as variable **INVCMT** in **datasets OCICMT and ADCM**. Datasets ADCM and OCICMT of the original database (safety follow-up) are located in CDROM subfolder 3_Datasets and Programs\3.2_Original database safety follow-up. Dataset ADCM is additionally located in CDROM subfolder Attachment 5A.*

CSLB Response 5B3a:

CDROM subfolder Attachment 5B3a contains copies of the actual hospital medication records/source data (including English translations of information relevant to concomitant medication) for the 28 subjects receiving any prohibited concomitant medication during the specified time period between 5 hours before and 24 hours after administration of randomized study medication.

For all subjects whose medication records/source data were compared with original CRF entries, CSLB has generated a listing that includes the information from the hospital medication records/source data, the corresponding original CRF entries, and the investigators' responses to the queries (Listing 5B3b_CM track changes database 08APR09.xls in CDROM subfolder Attachment 5B3b; also see CSLB Response 5B3b). Details on the outcomes of the source data review are included in the Reviewer Guide to the Database (location: CDROM subfolder 3_Datasets and Programs\3.1_Reviewer Guide to Database).

CSLB Response 5B3b:

As requested in CBER Comment 5B3a, the hospital medication records/source data to confirm the actual times of administration were collected from all subjects who received “any rescue medication” and “non-permitted medications” included in dataset PROHMED.xpt (i.e., the prohibited concomitant medication list for the additional robustness analysis conducted to address CBER Comment 5C) and documented as “ongoing” on the prior/concomitant medication CRF (location of PROHMED.xpt: CDROM subfolder Attachment 5B3b).

The requested table

(Listing_Q5B3b_Listing_medications_according_PROHMED.xpt) showing the actual dates and times of administration of “any rescue medication” and “non-permitted medications” is located in CDROM subfolder Attachment 5B3b. The corresponding data are contained in dataset CRL_Q6BR (location: CDROM subfolder 3_Datasets and Programs\3.3_Robustness analysis and also in CDROM subfolder Attachment 6\revised data robustness analysis).

The comparison of the actual hospital medication records/source data to the corresponding original CRF entries and investigators’ responses to the queries resulted in changes to the database. About 75% of these changes related to general comments concerning the availability of hospital records/source data and data management comments (see Listing 5B3b_CM track changes database 08APR09.xls in CDROM subfolder Attachment 5B3b; Note: In the revised database ADCM, the general comments are incorporated as variable TX, and the data management comments as variable DMCMT [CDROM subfolder 3_Datasets and Programs\3.3_Original analysis (revised database)\Datasets and 3_Datasets and Programs\3.4_Robustness analysis (revised database)\Datasets]).

Note: Any additional data changes implemented since the previous database closure are also included in Listing 5B3b_CM track changes database 08APR09.xls for completeness.

Reviewer Comment

Inspection of Listing Q5b12.pdf from amendment 25 reveals that a large number of the investigator query forms which stated that (discouraged/non-permitted) medications had not been used between the start of study attack or the start of study medication and 24 hours after treatment were received

by the sponsor after considerable delays from the date of randomized blinded administration of study medication. This calls into question whether the investigator would be able to accurately recall this information after such a significant time delay. Examples of the differences in time between randomization and the receipt of the investigator query form:

[illegible]

- 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.

Sponsor’s Response

CSLB Response 5C:

CSLB considers this additional requested analysis to be an exploratory robustness analysis of the primary endpoint. As stated in the Cover Letter and in CSLB Responses 5A and 10, CSLB’s and outside consultants’ position is that non-narcotic pain medications are ineffective for the treatment of acute HAE attacks and do not confound the interpretation of the primary endpoint. Consequently, these medications were not excluded/prohibited in the study protocol.

Result of the Additional Robustness Analysis

The additional robustness analysis conducted to address CBER Comment 5C clearly confirms the result of the original analysis of the primary endpoint, with a p-value of 0.014 in the primary Wilcoxon test in favor of the Berinert 20 U/kg group compared to placebo (see Table 11.17.1 in Tables_Q5c_robustness in CDROM subfolder Attachment 5C). However, the sensitivity of this additional robustness analysis decreased by imputing an additional 18.5% of the overall ITT study population to a poor/failure outcome (i.e., in addition to the 27.4% of the original analysis).

The complete dataset for the additional robustness analysis as well as the letters from the outside consultants are located in CDROM subfolder Attachment 5C (Tables_Q5c_robustness, Figures ageffkm_new_original and ageffkm_new_robustness; letters from consultants: statement --b(4)--, statement -b(4)-, statement -b(4)-).

Reviewer Comment

The sponsor has presented no data to substantiate its position that non-narcotic analgesics have no effect whatsoever on the intensity of any HAE attack symptom. In the absence of such actual data, the conservative approach is to impute a “poor/failure” outcome of 24 hours for subjects who were documented to have received such medications between 5 hours prior to ToS and ToSRel.

- 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, “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: TTREL = 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.

Sponsor’s Response

CSLB Response 5D:

For clarification of missing values of the variable TOANALG, please refer to CSLB Response 5A.

The impact of prohibited concomitant medications on the primary efficacy variable and on the per protocol (PP) population and sub-populations was determined as follows:

- *Narcotic Pain Medications:*
Narcotic pain medications, as listed in Appendix IVa of SAP Version 2.0 for the final analysis, only resulted in imputation of a poor/failure outcome of the primary endpoint under the following conditions:
 - *If they were administered in the critical time period between start of randomized study medication and start of symptom relief, or 24 hours after start of randomized study medication*
 - or*
 - *If they were recorded on the CRF as prior to and ongoing after the start of study medication and there was no investigator comment (variable INVCMT) to confirm that the medication was not used during the critical time period.*

- *Androgens, Tranexamic Acid and Aminocaproic Acid:*
The review of the closed database (based on the SAP Version 2.0 for the final analysis) confirmed that there were no changes in the dosing regimen of any of these medications during the critical time period between start of study medication and start of symptom relief in any subject. Therefore, according to protocol, none of these medications resulted in the imputation of a poor/failure outcome of the primary endpoint.
Note: Androgens [variable SGANDROG] led to exclusion from the PP analysis if they were administered within 4 hours after the start of blinded study medication and if they had not been used, or used at lower doses, before the study.

- *C1-INH and FFP (coded as “Plasma protein concentrate”):*
Two subjects (----b(6)----) received FFP as concomitant medication prn, documented as “prior” and “ongoing” on the CRF. However, in both cases, the investigator response to a query confirmed that FFP was not administered during the critical time period between start of study medication and onset of relief (see file DCFs_site8_USA in CDROM subfolder Attachment --b(6)----). Therefore, the use of FFP did not lead to imputation of a poor/failure outcome.
All open-label C1-INH administrations documented in the concomitant medication CRF started more than 24 hours after start of study medication and therefore did not lead to imputation of poor/failure outcome of the primary endpoint (see CSLB Response 11).

- *Drugs Targeting the Biological Mechanisms of Action of C1-INH:*
The review of the closed database (based on the SAP Version 2.0 for the final analysis) confirmed that no subject received “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.”

Note: The definitions and calculations of the primary endpoint TtRel+ (variable TTRELP) are provided in the Reviewer Guide to the Database

(location: CDROM subfolder 3_Datasets and Programs\3.1_Reviewer Guide to Database).

Reviewer Comment

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.

Sponsor's Response

CSLB Response 6:

The derivation of the primary endpoint is a 2-step process. During Step 1, the onset of symptom relief (i.e., variables TOSREL and TTREL) is determined based on the subject's assessment of the HAE attack under study. During Step 2, the imputation of the primary endpoint TtRel+ is performed based on the use of blinded rescue study medication, open-label emergency study medication, and prohibited concomitant medications. In order to facilitate validation of this 2-step process and to avoid an overly complex dataset, CSLB considered it necessary to create two datasets (CRL_Q6A, CRL_Q6B) in response to CBER Comment 6. CSLB provides the dataset for Step 2 in the following three versions: CRL_Q6BO for the original analysis, CRL_Q6BR for the additional robustness analysis, and CRL_Q6c containing both datasets for comparison. These datasets are located in CDROM subfolder Attachment 6.

An algorithm for derivation of the primary endpoint TtRel+ based on the variables in datasets CRL_Q6A, CRL_Q6BO and CRL_Q6BR is provided in the Reviewer Guide to the Database (location: CDROM subfolder 3_Datasets and Programs\3.1_Reviewer Guide to Database).

From the latter document:

In order to compare the differences in the imputation of the primary endpoint variable TTRELP between the original analysis and the additional robustness analysis conducted to address CBER's Comment 5C of the Complete Review Letter, a new dataset CRL_Q6C

was created. This dataset combines the classification of the concomitant medications according to Appendix IVa of the final SAP Version 2.0 of 26 October 2007 (variable CATEGORY) as well as the classification according to the extended list PROHMED.xpt for the additional robustness analysis (variable RCAT). For comparison, both primary endpoints TTRELP for the original analysis and RTTRELP for the additional robustness analysis are available in dataset CRL_Q6C.

Reviewer Comment

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

Sponsor's Response

The blind was broken on 2 November 2007 in compliance with the Standard Operating Procedures of the biometrics service provider, Accovion.

Reviewer Comment

The date given by the sponsor for unblinding of the pivotal trial was just 7 days following the date of SAP version 2.0.

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.

Sponsor's Response

Reviewer Comment

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.)

Sponsor's Response

Reviewer Comment

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.

Sponsor's Response

Reviewer Comment

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.

Sponsor's Response

Reviewer Comment

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.

Sponsor's Response

Reviewer Comment

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).

Sponsor's Response

Reviewer Comment

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.

Sponsor’s Response

Reviewer Comment

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.

Sponsor’s Response

Reviewer Comment

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.

Sponsor's Response

Reviewer Comment

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”.

Sponsor's Response

Reviewer Comment

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.

Sponsor's Response

Reviewer Comment

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.

Sponsor's Response

Reviewer Comment

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 Cagungan 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.

Sponsor's Response

Reviewer Comment

- 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.

Sponsor's Response

Reviewer Comment

- 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.
- 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.

Sponsor’s Response

Reviewer Comment

- 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.

Sponsor’s Response

Reviewer Comment

- 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.

Sponsor's Response

Reviewer Comment

- 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.

Sponsor's Response

Reviewer Comment

- We note that the variable “SGANAN” (SG [subgroup] with/without analgesics/anti-emetic-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 in analyses of the study’s primary efficacy endpoint. Please clarify.

Sponsor’s Response

Reviewer Comment

- 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.

Sponsor’s Response

Reviewer 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)

Sponsor's Response

Reviewer Comment

- 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.

Sponsor's Response

Reviewer Comment

- 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).

Sponsor’s Response

Reviewer Comment

- 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.

Sponsor's Response

Reviewer Comment

- 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 October 26, 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

(iii) 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.

Sponsor's Response

Reviewer Comment