

# Memorandum Telecon with Fresenius Kabi - 6/18/2007 - Voluven

- **Memorandum**

**DATE:** June 19, 2007

**FROM:** Cheryl Campbell, CBER/OBRR/DBA, HFM-380

**TO:** DBA File: CRMTS # 6233 Fresenius Kabi

**Subject:** NDA BN070012: Clinical and PK Discussion

**Meeting Date:** June 18, 2007

**Time:** 9:30 - 10:30 AM

**Location:** WOC 1 - Telecon

**Type of Meeting:** Type C Meeting

**Fresenius Kabi Participants:**

Frank Bepperling

Cornelius Jungheinrich

Jeanette Neumann

Karin Heimdahl

Astrid Schaefer

**Carolina Research**

W. Gerald Coln

**CBER Participants:**

Cheryl Campbell

Elena Karnaukhova

Laurence Landow

Iftekhar Mahmood

**Meeting Objective:** To discuss clinical and PK issues for the NDA.

**Highlights:**

Responses from Fresenius Kabi in **bold** follow the CBER questions:

**Clinical:**

1. Why are there ~50% of values missing for the LFT shift tables at 24 hrs.

**Sponsor response:** These data are not actually missing, but rather, were not captured in 8 of 21 studies.

**CBER also inquired whether LFTs were captured at study times > 24 h. The sponsor stated that all available data can be found in Table 99. The one subject with an ALT of 1200 experienced multi organ failure.**

2. Why are there no 24 h data for the LFTs shift tables in the HES 130 Total, HES 200, and all Control arms.

**Sponsor response:** There are data for only 14 of 21 studies. LFT data for the US study were not captured at 24 hours. However, there are shift tables for the US study in the final study report.

**CBER noted that Clinical Lab #4 reported the ALT upper limit of normal = 20 and wanted to know if this was accurate. The sponsor was not sure and stated they would get back to CBER with a definitive answer.**

3. Why aren't there LFT data for the sponsor's test product, 6% HES 130/0.4, comprising ~40% of the HES 130 Total, for which there are data.

**Sponsor response: The sponsor noted that for safety reasons, they reported the % for all HES 130 products and not just the 6% product. They also noted there are data for the 130/0.4 cohort on the CD Rom in Tables 11.1 and 11.2.**

4. Please indicate the volumes containing the LFT and serum creatinine raw data, since the Summary Tables do not indicate this.

**Sponsor response: These data (lab values) are on the CD Rom.**

5. Module 2.7 table 101 lists serum creatinine values for HES 130 Total. Please submit corresponding values stratified by type of HES 130 solution.

**Sponsor response: These data are on the CD Rom in Tables 11.1 and 11.2.**

6. Why are up to 38% of values for serum creatinine shift tables missing from table 102?

**Sponsor response: The response is similar to the response to the LFT data. A total of 6 out of 21 studies did not measure serum creatinine.**

**CBER inquired as to the longest study time serum creatinine was measured post infusion. The sponsor stated one month, in study HS-13-25-CH, which had 31 subjects. CBER inquired if any studies measured serum creatinine after 1 day. The sponsor was not sure and promised to follow-up on this question.**

**CBER stated their review will focus heavily on serum creatinine, since it is projected that the product will be used in ICU patients, most of whom will be renally compromised.**

**The sponsor noted that in study HS-13-36-FR, gelatin was used as a control and that creatinine clearance and other renal parameters were captured (N=65).**

**CBER inquired why the study had been stopped for patients with septic shock. The sponsor stated that there was a problem with recruitment and the study protocol was very complicated.**

7. Please submit (or indicate in the current submission) final serum creatinine values for each age cohort found in tables 103-108.

**Sponsor response: This information has not yet been calculated. The sponsor will provide the data in the formal response to the submission by June 26, 2007.**

## **PK**

1. Provide the method of calculation of half-life in single and multiple dose study.

**Sponsor response: The sponsor used----- . They plan to provide the calculations.**

2. There is a discrepancy in the PK parameters in the study with renal impairment between compartmental and non-compartmental analysis. Please explain this discrepancy.

**CBER noted a discrepancy in tests of renal impairment between the dependent and independent models. The half-lives are different, which should not happen.**

**Sponsor response: This discrepancy is considered normal for this type of product because it is a mixture and it changes over time. The sponsor noted**

that CBER should read a 2005 publication on this issue provided in the submission. It notes that different parts of the curve are weighted differently. CBER inquired how this would be addressed in the labeling. The sponsor stated that the half-life is not affected by renal dysfunction. CBER noted a doubling of the half-life from 5.6 to 11.7 h. The sponsor replied that in study 1328, there are subjects with mild, moderate, and severe renal dysfunction, which accounts for the different half-lives reported.

CBER noted that based on compartmental analysis, the half-life of 6% HES-130/0.4 is 2 times longer in patients with severe renal impairment than in normal subjects. On the other hand, non-compartmental analysis showed no difference in half-life between the two groups.

The sponsor stated that a review of the submitted literature may clarify some of CBER's concerns. CBER stated they believed the true half-life was 7-9 hours, and recommended that the accumulation ratio be used, i.e., the AUC of the first dose and the AUC of the last dose, in the recommended formula. The resultant half-life will be close to that of a single dose.

CBER inquired as to the name of the software program used for the PK calculations. The sponsor stated that they used-----.

CBER further inquired whether the sponsor could provide raw data for the renally-impaired subgroup, including body weight, age, dose, and creatinine clearance. In addition, CBER requested another table that includes plasma concentration vs. time and the PK parameters generated, for each subject.

CBER stated that the sponsor should provide the PK data in arithmetic mean and not geometric mean. The sponsor promised to comply.

#### **Other discussion:**

CBER inquired whether there were any ongoing studies using the product. The sponsor stated there were two: one in subjects with severe sepsis and another comparing the test product to crystalloid solution in subjects undergoing hemodialysis. There are 2 x 90 subjects in the sepsis trial and 8 subjects in the hemodialysis trial.

CBER noted that albumin often is used to treat hypotension in dialysis patients, and that an albumin shortage might result in increased off-label use of 6% HES 130 for this purpose, which would constitute a public health concern. CBER advised the sponsor to consider enlarging the sample size of the hemodialysis trial, and that in any event, a post marketing commitment might be requested to address these questions.

The sponsor stated they did not believe the product was used extensively to treat subjects undergoing hemodialysis in countries where it is already licensed.

CBER inquired whether the sponsor had data to support this viewpoint. The sponsor will provide an answer to CBER in the near future.

#### **Action Items:**

- Fresenius plans to provide a formal response to the questions by June 26, 2007.
- Fresenius will determine if serum creatinine was measured past 1 day.
- Fresenius will determine if there are data to support the view that this product is not used extensively in hemodialysis patients.