Statistical Review and Evaluation
(Final Memorandum)

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Sponsor:	Fresenius Kabi
Product:	Voluven®
Indication:	Treatment and prophylaxis of hypovolemia
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Executive Summary

This post marketing commitment (PMC) was a multi-centre, randomized, controlled, parallel-group, double-blind trial to evaluate the efficacy and safety of Voluven vs. HSA in volume substitution therapy during open heart surgery in 2 to 12 year old pediatric patients. The primary efficacy endpoint was the total volume of colloid solution in mL/kg required for intraoperative volume replacement therapy. Equivalence between the two treatment groups regarding the primary efficacy endpoint was established in both the PP population (n=29 for Voluven and n=26 for HSA) and ITT population (n=31 for Voluven and n=30 for HSA).

Seventeen patients (54.8 %) in the Voluven group and eight patients (27.6 %) in the HSA group had adverse events (AEs) with a potential relationship to the study drug assessed by the investigators. Mostly, the system organ class metabolism and nutrition disorders (45.2 % in the Voluven group and 17.2 % in the HSA group) was affected, and in particular with respect to hypoproteinaemia (32.3 % in the Voluven group but none in the HSA group). Eight of the ten patients with hypoproteinaemia were male and only two of them were female with a p-value of 0.017 by Fisher's Exact test. The sponsor responded that this potential gender difference could not be confirmed in other trials conducted with Voluven and had to be regarded as an incidental finding.

1. Background

The Voluven (6% HES 130/0.4) has been approved for therapy and prophylaxis of hypovolaemia in many EU member states since 2000. Regulatory approval for pediatric

patients became effective in January 2004 in Europe. Voluven was approved in the USA under NDA BN070012 on December 27, 2007 with two PMCs. According to the recommendation of the Pediatric Review Committee, this PMC was to conduct a clinical study of the efficacy and safety of 6% HES 130/0.4 vs. 5% HSA in volume substitution therapy during open heart surgery in 2 to 12 year old pediatric patients,

With this submission the sponsor provides the final clinical study report. This memo serves as the final review of the PMC.

In the original submission, the sponsor did not include datasets needed for the complete review. Per FDA's request, the datasets with the associated statistical analysis programs were submitted on June 9, 2011.

2. Clinical Study Protocol

This PMC was a multi-centre, randomized, controlled, parallel-group, double-blind trial to evaluate the efficacy and safety of Voluven vs. HSA in volume substitution therapy during open heart surgery in 2 to 12 year old pediatric patients. HSA was the control drug which had been proven to effectively treat hypovolaemia and to restore and maintain haemodynamics.

Randomization was stratified according to the two different total extracorporeal circulation (ECC) volumes (400 mL or up to 800 mL) which took into account the patient's body weight. The investigator, the surgeon and nurses were kept blinded. The only unblinded person was the perfusionist. The administration of study drug was done by the anaesthetist and partly by the perfusionist who filled the ECC bypass machine. A patient received either Voluven or HSA intraoperatively.

The study was conducted at two centers in Austria and Belgium. It was intended to include a total of 60 patients (30 per treatment group) in the study. Actually, 61 patients were randomized and 60 patients were treated with either the investigational drug or the control drug. The study consisted of the following population sets:

- **Intent-to-Treat (ITT):** all randomized patients.
- **Per-Protocol (PP):** all patients in the ITT population who had no major protocol deviations which is the primary analysis set.
- **Safety (SAF):** all patients who were treated with study drug. The safety and ITT population in this study were identical except for the one patient who was randomized but not treated with study medication due to aspirin intake prior to surgery.

The following time points during the course of the study were defined:

Screening: within 14 days before surgery

T0: baseline immediately after induction of anaesthesia

T1: immediately before ECC

T2: immediately after protamine application

T3: after skin closure

T4: arrival on the intensive care unit (ICU) (after complete installation)

T5: postoperative period on ICU: 1st post-op morning

T6: 2nd post-op morning

T7: ICU discharge

Follow-up visit: 28 days after discharge from operating room

3. Study Results

The first patient entered the study on March 31, 2009 and the last patient completed the study on August 5, 2010. A safety review committee/data monitoring committee was not constituted.

3.1. Study patients

3.1.1. Disposition of patients

The patient disposition is summarized below based on sponsor's Table 14.1.1.

Table 14.1.1: Summary of patient disposition

Disposition of patients	Voluven	HSA
Randomized (ITT)	31	30
Treated (SAF)	31	29
PP	29	26
Completed study	26	26
Prematurely withdrew from study	5	3
Protocol violation	5	3
Adverse event	0	0
Consent withdrawn	0	0
Death	0	0
Day 28 follow-up performed	31	29

The following subjects had protocol deviations leading to exclusion of PP based on sponsor's Table 14.1.4.

Table 14.1.4: Listing of exclusions from analysis populations
Population: ITT

Protocol deviations	Voluven	HSA
Rescue colloid was administered before study drug HSA been applied	-b(6)-	-b(6)---- --------
Intraoperative volume replacement could not be fully documented	-b(6)-	
Rescue colloid HSA been administered and total dose of study drug was lower than 48.5 mL/kg body weight		--b(6)--- --------
Aspirin taken within 14 days prior to surgery		-b(6)-

3.1.2. Demographic and other baseline characteristics

Patients in the Voluven group were slightly older (mean 5.2 with range of 2-12 vs. 4.0 with range of 2-9) and consequently taller and heavier. The p-value for age was at a trend level of 0.076. The risk of surgery was assessed by applying the RACHS-1 risk score. The percentage of patients in category 1 was greater in the HSA group (Voluven 16.1 %, HSA 31.0 %). Overall, the treatment groups were comparable regarding demographic data and other baseline characteristics.

3.2. Efficacy

3.2.1. Primary efficacy endpoint: total volume of colloid solution in mL/kg required for intraoperative volume replacement therapy

In the PP population, the mean volume of colloid solution required intraoperatively was 36.60 mL/kg body weight (SD = 11.76) in the Voluven group and 36.97 mL/kg body weight (SD = 11.86) in the HSA group. This endpoint was tested as follows:

$$H_0: \mu_{\text{Voluven}} \leq 0.55 \times \mu_{\text{HSA}} \quad \text{or} \quad \mu_{\text{HSA}} \leq 0.55 \times \mu_{\text{Voluven,}}$$

where μ_{Voluven} was the mean infused volume of Voluven and μ_{HSA} was the mean infused volume of HSA. This corresponded to an equivalence range of (0.55, 1.82) for the ratio $\mu_{\text{Voluven}} / \mu_{\text{HSA}}$. The null hypothesis was tested by calculating a two-sided 95% confidence interval for the ratio according to the method of Fieller based on an ANOVA including treatment and centre as effects. The ANOVA results for the PP population (which was the population of primary interest) and the ITT population are presented in sponsor's Table 4 below.

Table 4: ANOVA result for total volume of study drug plus rescue colloid (mL/kg body weight) and confidence interval for the ratio of means (ITT and PP population)

	Voluven		HSA		
Population	N	Least squares mean (SEM)	N	Least squares mean (SEM)	Ratio Voluven/HSA (95% CI)
PP	29	37.70 (2.18)	26	38.33 (2.33)	0.98 (0.84;1.16)
ITT	31	38.11 (2.62)	30	40.48 (2.68)	0.94 (0.78;1.13)

This reviewer confirmed the summary statistics included in the Table 4. It shows satisfactory efficacy results for the equivalence between Voluven and HAS in both PP and ITT population.

The influence of centre was statistically significant for the PP population (p=0.0360), and the ITT population (p=0.0241). An additional analysis was done including treatment by centre interaction. The interaction effect had no significant influence (p=0.976) in the PP population and ITT population. Thus it was concluded that the interaction effect was negligible compared to the effect of centre.

3.2.2. Secondary efficacy endpoints

Overall, the two treatment groups had similar results regarding the secondary efficacy endpoints, including haemodynamic parameters, fluid input, ECC priming components, fluid output, vasoactive and inotropic drugs.

Fluid balance was calculated as the difference of fluid input and output. In the mean, balance in mL/kg body weight was higher, i.e. more positive, for HSA for overall time and in particular for the intraoperative period until arrival on ICU (T0– T4, explorative p-value: 0.047). The analysis in the ITT population showed similar results. The results are shown in sponsor's Table 8 below:

Table 8: Fluid balance in mL/kg body weight (PP population)

	Voluven (N=29)				HSA (N=26)			
	N	Mean	SD	Range	N	Mean	SD	Range
Fluid balance								
T0 - T4	29	15.38	22.89	-70.2-55.6	26	27.66	21.55	-3.4-77.2
T4 - T6	29	35.21	45.93	-11.3-183.1	26	37.97	48.06	-35.7-213.0
Overall time	29	51.28	47.46	3.3-196.9	26	67.07	62.57	-12.2-278.9

3.2.3. Handling of dropouts or missing data

Patient –b(6)- was randomized, but the surgery was postponed due to sudden illness on the day of the surgery. The patient received the new patient number –b(6)- later on and was analyzed and listed using –b(6)- only. The data collected for –b(6)- were kept in the datasets, but neither analyzed nor listed.

Patient –b(6)- was randomized, but withdrawn from the study when the anaesthesiologist recognized that aspirin treatment was stopped too late according to study protocol section 11.8.7. For this patient only screening data were available. The patient was kept in the ITT population and analyzed for the primary efficacy parameter with a volume of 0 mL.

For patient –b(6)-the patient file was lost. Information about concomitant medication, fluid input, fluid output, haemodynamics and possibly AEs after T4 could only be partially recorded. This patient was excluded from the PP population, but the available data were analyzed for the ITT population and safety population. Perioperative blood cell loss was also calculated since the Hct measurements at T0 and T6 were available and RBC transfusions at ECC priming were reported. Between T0 and T6 the volume of RBCs was set to 0 mL.

3.3. Safety

3.3.1. AE

An overview of treatment emergent AEs is given in sponsor's Table 10:

Table 10: Overview of adverse events (Safety population)

	Voluven (N=31)	HSA (N=29)
	N (%)	N (%)
Any AE	30 (96.8)	29 (100.0)
Any serious AE	11 (35.5)	7 (24.1)
Any AE with maximal grade 5 (death)	0 (0.0)	0 (0.0)
Any AE with maximal grade 4 (very severe)	7 (22.6)	4 (13.8)
Any AE with maximal grade 3 (severe)	19 (61.3)	13 (44.8)
Any AE leading to discontinuation of study drug	0 (0.0)	0 (0.0)
Any AE related to study drug	17 (54.8)	8 (27.6)
Any AE related to study procedure	9 (29.0)	6 (20.7)

No AE lead to discontinuation of study drug. No patient died in this study. No SAE was evaluated as related to study medication, according to the sponsor.

Largest treatment group differences were seen in the following MedDRA system organ classes: gastrointestinal disorders (67.7% in Voluven vs. 37.9% in HSA), metabolism and nutrition disorders (87.1% in Voluven vs. 65.5% in HSA), vascular disorders (45.5% in Voluven vs. 34.5% in HSA), injury, poisoning and procedural complications (38.7% in Voluven vs. 27.6% in HSA), infections and infestations (16.1% in Voluven vs. 34.5% in HSA). The most obvious difference occurred for the preferred term hypoproteinaemia which occurred in 32.3% of the Voluven patients but in none of the HSA patients.

3.3.2. AE with causal relationship to study medication

Seventeen patients (54.8 %) in the Voluven group and 8 patients (27.6 %) in the HSA group had AEs with a potential relationship to study drug as assessed by the investigators. Mostly, the system organ class metabolism and nutrition disorders (45.2 % in the Voluven group and 17.2 % in the HSA group) was affected, and in particular hypoproteinaemia (32.3 % in the Voluven group only) contributed to this proportion between Voluven and HSA.

4. Reviewer's Additional Analyses

4.1. Age effect

As the sponsor calculated, the p-value for age by treatment groups was 0.076 at a trend level. The detailed distribution is presented in the table below.

Age (years old)	Voluven (N=31)	HAS (N=30)	Total
2	7	8	15
3	2	5	7
4	6	10	16
5	7	2	9
6	1	1	2
7	1	1	2
8	2	1	3
9	2	2	4
10	1	0	1
12	2	0	2

Regarding the primary efficacy endpoint, after adjusting for the age effect, the difference between the two treatment groups was even smaller.

For the ten Voluven patients with AE of hypoproteinaemia, it appeared that hypoproteinaemia occurred more often in male pediatric patients with a p-value of 0.017 by Fisher's Exact test.

Voluven (N=31)	Male	Female	Total
Hypoproteinaemia	8	2	10
No hypoproteinaemia	7	14	21
Total	15	16	31

4.2. Centre effect

Regarding the primary efficacy endpoint analysis, the influence of centre was statistically significant for the PP population and the ITT population. However, the treatment difference was consistent within each centre (see Table below). As pointed out by the sponsor, the treatment by centre interaction effect had no significant influence (p=0.976) in the PP population and ITT population. Therefore, the centre effect is not a concern in this study.

Results of primary efficacy endpoint by centre and treatment (PP)				
		N	Mean	SD
Site 1	Voluven	19	34.13	12.25
	HAS	18	34.83	11.58
Site 2	Voluven	10	41.29	9.63
	HAS	8	41.79	11.77

5. Communication with Sponsor:

On July 11, 2011, the following comment was sent to the sponsor via email:

"For the ten subjects with hypoproteinemia in the Voluven treatment group, eight were male and only two of them were female. Please comment on whether a gender difference for this parameter has been noted in previous trials using Voluven."

On July 20, 2011, the sponsor submitted response to this comment under IND 9740 serial # 42. The response is summarized below:

- In 21 Voluven trials conducted until 2005, no such gender difference was observed with regard to the Adverse Event hypoproteinemia. In total, only 3 cases (0 in male subjects, 3 in female subjects) of hypoproteinemia or total protein decreased were reported in the groups treated with Voluven.
- In the Post-marketing Commitment (PMS) study 06-HE06-01 (Title: "Crystalloids or colloids in patients with severe sepsis: effects on hemodynamics and tolerability of enteral nutrition"**)** submitted to the Agency on April 21, 2011, 31.3% males and 27.8% females had treatment emergent hypoproteinemia among the total 64 males and 36 females treated with Voluven respectively.
- A potential gender difference with regard to the Adverse Event hypoproteinemia which was observed in this study could not be confirmed in the other trials conducted with Voluven and has to be regarded as an incidental finding.

After confirming with the medical reviewer, the sponsor's response is considered to be acceptable.

6. Conclusions and recommendation:

1) This PMC study met the success criterion for the primary efficacy endpoint. The results were verified by this reviewer.

2) Although patients in the Voluven group were slightly older than the patients in the Control group with a p-value at a trend level of 0.076, the primary efficacy endpoint point analysis was not impacted after adjusting for the age effect.

3) In the primary efficacy endpoint analysis, centre was statistically significant for the PP population and the ITT population. However, based on the fact that the treatment difference was consistent within each centre, the centre effect is not a concern in this study.

4) For the safety analysis, a gender difference with regard to the AE hypoproteinemia was observed in subjects treated with Voluven. Eight of these ten patients with hypoproteinaemia were male and only two of them were female with a p-value of 0.017 by Fisher's Exact test. The sponsor responded that this potential gender difference with regard to hypoproteinemia could not be confirmed in the other trials conducted with Voluven and had to be regarded as an incidental finding. The sponsor's response is considered to be acceptable.

5) More serious adverse events (SAEs) were observed in the Voluven group than the HSA group (11 vs. 7, or 35.5% vs. 24.1%). According to the sponsor, no SAE was evaluated as related to study medication.

6) Statistical issues identified in the safety endpoint analysis are reasonably addressed by the sponsor.