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Through	Toby Silverman MD, Chief, Clinical Review Branch
Sponsor	Fresenius Kabi Deutschland GmbH
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RPM	Cheryl Campbell/Franklin Stephenson
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EXECUTIVE SUMMARY

Background

The only hydroxyethyl starch (HES) solution marketed for plasma volume expansion is hetastarch (**6% HES 450/0.7**). Hetastarch is a *high* MW (450 kDa) HES solution with a *high* degree (0.7) of hydroxyethyl group substitution on the C₂, C₃, and C₆ of glucose units of the starch polymer (amylopectin). The investigational HES in this NDA, **6% HES 130/04**, has a *lower* molecular weight and *lower* degree of substitution.¹

Differences in MW and HES substitution have important implications with respect to pharmacokinetics and clinical pharmacology. The higher the MW, the slower the metabolism by plasma α -amylase and the longer the product remains within the circulation. Attaching HES groups to glucose units at carbon positions 2, 3, and/or 6 has the same effect.

Thus, compared to hetastarch, 6% HES 130/0.4 has a **shorter half-life**, exhibits **less accumulation in plasma**, is **hydrolyzed more quickly** by serum α -amylase, and is **excreted more quickly** by the kidneys.

Because starch polymers are comparatively large molecules, even so-called medium MW HES products (130 kDa) such as 6% HES 130/0.4 expand and maintain plasma volume more effectively than crystalloid solutions used for this purpose. However, the maximum labeled dose of hetastarch that can be administered to the average adult for treatment of hypovolemia within a 24 h period is 1500 mL (20 mL/kg). The reason for this ceiling is that hetastarch impairs hemostasis by lowering **factor VIII activity** and **von Willebrand factor (vWF) antigen concentration**. An HES solution as effective as hetastarch but with an improved hemostatic profile would be of considerable benefit in patients undergoing major surgery. If such a solution was rapidly eliminated despite renal dysfunction, it would be especially beneficial for hemodynamically unstable ICU patients.

6% HES 130/0.4 has been used widely in Europe — approximately 7,800,000 patients have been treated with the product — since it was approved in the late 1990s. During this time, 148 safety events have been reported to the sponsor, most of which occurred during clinical trials. The sponsor has assessed 73/148 of these adverse events as

¹The sponsor also manufactures 2%, 4% and 10% HES 130/0.4 as well as 6% HES 200/0.5, but indications for these products are not part of this NDA.

Current submission

SAEs possibly or probably related to product administration.

This NDA includes data from studies supporting licensure in Europe and data from the single US study in subjects undergoing orthopedic surgery. These studies are as follows:

(a) Phase 1 single-dose (N=24) and multiple-dose (N=12) PK and PD studies in volunteers;

(b) Phase 1 PK studies in **renally-impaired subjects who are NOT dialysis-dependent** (N=19) showing slightly increased AUC, but comparable terminal half-life to healthy volunteers;

(c) Phase 2 efficacy (hemodynamic) studies in subjects undergoing elective surgery (N=72) showing similar volumes are required to maintain hemodynamic stability compared to control (**6% HES 200/0.5**);

(d) Studies in subjects (N=82) <2 years old undergoing non-cardiac surgery;

(e) **Phase 3 supportive studies** (N=3) comparing efficacy² (vital signs, urine output) and safety (RBC transfusion rate) of **6% HES 130/0.4 vs. 6% HES 200/0.5** in patients undergoing orthopedic surgery (N=152) and cardiac surgery (N=59) showing reduced need for allogeneic RBC transfusion but comparable overall RBC transfusion rate;

(f) **A pivotal Phase 3 trial** (N=100) conducted for US licensure which met its prospectively defined non-inferiority endpoint compared to 6% HES 450/0.7 in terms of volume expansion, associated with reduced need for allogeneic RBC transfusion;

(g) Supporting safety data from 4 controlled studies in subjects (N=346) with stroke or sudden hearing loss who were randomized to receive 10% HES 130/0.4 vs. 6% HES 200 for up to 10 days;

(h) A supporting safety study comparing the effect of 6% HES 130/0.4 vs. 3% gelatin solution on postoperative renal function in subjects undergoing aortic surgery which found no between-group differences.

²Two of these supportive Phase 3 studies failed to meet their equivalence statistical margin, but the difference was not *clinically* meaningful, e.g., 35 mL.

Findings

1. Compared to hetastarch, 6% HES 130/0.4 is just as effective in expanding plasma volume, but associated with fewer bleeding events and a lower incidence of (a) SAEs in the aggregate, (b) AEs of severe intensity (especially in the 65-75 and >75 year old cohorts), and (c) AEs of the CNS, respiratory, and renal systems. Generally, speaking, Factor VIII and vWF levels recover more quickly after surgery and rebound to higher levels in subjects treated with 6% HES 130/0.4.
2. A randomized, controlled study (N=82) has been conducted in pediatric subjects undergoing elective surgery. Safety and efficacy are consistent with studies conducted in adult subjects.
3. No safety signal for worsening renal function is apparent in subjects with pre-existing renal dysfunction who receive 6% HES 130/0.4 (see next paragraph).

Putative Renal Toxicity?

A 2001 study from *Lancet* found that in 129 adult ICU patients with severe sepsis, HES 200/0.6 doubled ($p=0.03$) the risk of acute renal failure (defined as a two-fold increase in SCr or need for renal replacement therapy) when compared to 3% gelatin solution. Although the authors reported that "ARF" developed in more HES subjects than gelatin subjects (42% vs. 23%), mean SCr concentrations differed *only* on Days 6 and 7 (out of 28 days), and necessity for renal replacement therapy was *not different* (20 vs. 17% of subjects, HES 200 vs. control).

FDA's review of the line listings for all NDA subjects with pre-existing renal disease (i.e., abnormally elevated SCr at baseline) found *fewer* cases of treatment-emergent renal failure (MedDRA terms: renal dysfunction, renal failure acute, renal failure NOS) and oliguria in the 6% HES 130/0.4 treatment arm than in the control arm. This finding is limited by the comparatively small number of enrolled subjects with pre-existing renal dysfunction.

4. No multiple-dose studies have been conducted in hypotensive subjects with severe sepsis, where clinical use could be *substantial*.

Recommendation

Approval with a PMC for a multiple-dose RCT to be conducted in subjects with septic shock who have severe renal dysfunction, regardless of whether or not they are dialysis-dependent.

ADDENDUM: 7 DEC 2007

The sponsor has submitted a "Company Response" dated 30 November 2007 in which they commit to performing a multi-dose randomized controlled trial in subjects with severe sepsis including subjects with renal dysfunction and at risk for deterioration of renal dysfunction. They indicate that the final study report entitled "Crystalloids or colloids in patients with severe sepsis: effects on hemodynamics and tolerability of enteral nutrition" (short title: CRYSTMAS, study code 06-HE06-01) will be submitted within 36 months of the Approval Letter.

I have reviewed the final protocol for CRYSTMAS and it is acceptable.

1.0 BACKGROUND

Hydroxyethyl starch (HES) solutions differ widely in terms of mean molecular weight, molar substitution by hydroxyethyl groups on glucose units of the starch polymer, pattern of hydroxyethyl substitution (C_2/C_6 ratio), and concentration (6%). These differences have important clinical implications. For example, the higher the MW, the slower the metabolism and the longer circulatory residence time; attaching HES groups to glucose units at carbon positions 2, 3, and/or 6 has the same effect.

Thus, compared to hetastarch (6% HES 450/0.7), 6% HES 130/0.4 has a **shorter half-life**, exhibits **less accumulation in plasma**, is **hydrolyzed more quickly** by serum α -amylase, and is **excreted more quickly** by the kidneys.

Each liter of 6% HES 130/0.4 contains 60 g HES and 9 g NaCl and has a colloid osmotic pressure of 36 ± 4.1 mmHg.

1.1 Chronology

Pre-Phase 3 IND meeting on 29 August 2000

Sponsor presented data from studies conducted in Europe and reported the following:

- ▶ Animal studies support safety in pregnancy.
- ▶ The PK after infusion of 500 mL showed an initial serum half-life of 1.0 hr and terminal half-life of 12 hr.
- ▶ In a study of subjects with renal impairment, in 4 strata of CCr, there was delayed elimination but nearly total clearance observed at 24 hr.
- ▶ In CABG studies, vWF was higher than at baseline, which is not the case with HES.
- ▶ 3 Phase 1 and 6 clinical studies (total subjects treated with test product: 168), in which 14 subjects received ≥ 3000 mL of product, showed similar safety profiles for 6% hydroxyethyl starch 130/0.4 and pentastarch.

Phase 3 IND (Study HS-13-30-US) submitted 23 March 2001

- ▶ Placed on hold.

Letter to sponsor with recommendations sent on 30 May 2001

- ▶ At least 300 subjects treated with the test product are required to evaluate safety.
- ▶ The primary efficacy endpoint is a comparison of volumes of study colloids infused during surgery
- ▶ FDA does not consider coagulation assays to be validated surrogate markers for bleeding complications in surgery patients.
- ▶ Bleeding complications would be an acceptable safety endpoint.

Revised protocol submitted and accepted by FDA on 6 July 2001

Pre-NDA meeting held on 1 September 2004

- Discussion regarding *Lancet* study comparing 6% hydroxyethyl starch 200/0.6 versus gelatin in patients with acute renal failure in severe sepsis, in which the authors concluded use of 6% starch 200/0.6 as a plasma volume expander was an independent risk factor of ARF in septic shock patients.
- According to the sponsor, enrolling septic subjects in clinical trials has proved to be “logistically difficult”.
- The sponsor noted it had conducted safety trials in subjects with various degrees of renal impairment and found “no problems with clearance”.
- FDA requested that the sponsor submit all datasets to the NDA. The data should include safety information for the non-US and US studies.

1.2 Overview of Preclinical Toxicology

Rats and dogs received 9 g/kg body weight of 10% HES 130/0.4 per day for 13 weeks as a top-load and showed signs of increased workload, without specific mortality, toxicity, or organ damage. This is equivalent to 6300 mL per day for 13 weeks in a 70 kg adult, which is three times higher than the largest recommended human dose of 3 g/kg body weight.

Tissue storage was investigated using radiolabeled product administered to rats. Whole body tissue levels were lower when compared to HES 200/0.5 and far lower when compared to HES 450/0.7. These findings are consistent with results of PK studies.

No separate acute toxicity studies with 6% HES 130/0.4 were performed (see toxicology review memo).

1.3 Overview of Pharmacokinetics

The initial (distribution) half life ($t_{1/2\alpha}$) and terminal (elimination) half life ($t_{1/2\beta}$) of 6% HES 130/0.4 are approximately *one-quarter* that of hetastarch. Similarly, the AUC is more than an order of magnitude *lower* and the clearance 26-fold *greater* than 6% HES 450/0.7 (see table 1, below).

- In single dose study **HS-13-10-DE, healthy volunteers** (N=24) received a single dose of 500 mL 6% HES 130/0.4 (top-load subgroup) or 10% HES 130/0.4 (isovolemic subgroup) infused over 30 min.

In the top-load subgroup, blood and plasma volume increased by 20% and 32% (mean maximum values), respectively. In the isovolemic subgroup, blood and plasma volume increased by 7% and 21%, respectively. These effects lasted ~ 6 hr in each subgroup. Half-lives (α and β) were 1.39 and 12.1 hr for 6% HES

130/0.4 and 1.54 and 12.8 hr for 10% HES 130/0.4. Within 72 hr, 62% and 68% of administered drug was excreted after treatment with the two products. AEs such as headache, dizziness, and tachycardia, were reported in both treatment arms. No SAEs were reported.

- ▶ In multiple dose study **HS-13-11-DE, healthy male volunteers** (N=12) received 500 mL 10% HES 130/0.4 over 30 min on 10 consecutive days. Blood samples for PK analysis were drawn at Day 1 and 10. The observation period lasted until 72 hr after start of the last infusion, and follow-up extended for 6 weeks. Recovery rate in the urine was calculated to be 69% on Day 1 and 70% on Day 10. Half-lives were **1.21 hr (α) and 7.1 hr (β)** on Day 1, and **1.42 (α) and 21.9 hr (β)** on Day 10. Total plasma clearance was calculated as 23.9 mL/min on Day 1 and 22.0 mL/min on Day 10. No SAEs occurred during the study, but AEs were observed in 9 subjects during the study and 6 subjects during follow-up: 3 cases of pruritus appearing between Day 8-15 after the last infusion disappeared spontaneously after 10-17 days.
- ▶ PK after 500 mL of a single-dose of 6% HES 130/0.4 in **subjects with renal impairment** was investigated in **HS-13-28-DE**, a non-randomized, single-center study with 4 Cl_{cr} strata: 15 to <30, 30 to <50, 50 to <80, and 80 to <120 mL/min.

HES plasma concentrations were higher in the subgroup with Cl_{cr} <50 mL/min than in those with Cl_{cr} >50 mL/min. As expected, serum levels were somewhat higher in the 15-30 mL/min subgroup compared with the 30-50 mL/min subgroup. AUC and HES total plasma clearance depended on renal function, a relationship that was even stronger when controlling for age, body mass index, height, and weight. Subjects with Cl_{cr} <50 mL/min had, on average, a 73% larger AUC than subjects with Cl_{cr} >50 mL/min, although C_{max} was not affected by renal impairment.

Renal impairment did not affect terminal half-life (mean 16.1 hr, range: 15.5 - 17.2 hrs), **although distribution half-life was prolonged**, e.g., in subjects with Cl_{cr} between 80 and <120 mL/min, mean alpha half life was 0.6 hr compared to 1.5 hr in subjects with Cl_{cr} <50 mL/min. Corresponding results were obtained for drug elimination half-life from the central compartment (a two-compartment model provided a valid fit for the HES plasma concentrations). The overall incidence of AEs was low.

Only in subjects with Cl_{cr} <50 mL/min was there a pronounced increase in AUC, and even here, there was no effect on terminal half-life. Overall, therefore, there appears to be no contraindication

for a single infusion of 6% HES 130/0.4 in subjects with renal impairment as long as no oliguria or anuria is present.

Table 1: Pharmacokinetics of Various Hetastarch Solutions (source: sponsor)						
HES	Dose (g)	C _{max} (mg/mL)	t _{1/2α} (h)	t _{1/2β} (h)	AUC _{0-∞} (mg x h x mL)	Cl (mL/min)
450/0.7 (6%)	30	7.8	NA	>300	NA	NA
200/0.62 (6%)	30	5.2	5.08	69.7	NA	1.23
200/0.5 (10%)	50	8.0	3.35	30.6	NA	9.24
200/0.5 (6%)	30	6	NA	NA	NA	4.88
130/0.4 (6%)	26.3	3.7	1.39	12.1	14.3	31.4
130/0.4 (10%)	44.1	6.5	1.54	12.8	28.8	26.0

2.0 EFFICACY RESULTS

2.1 Clinical trial roster and populations studies

The sponsor has submitted data from **21 clinical studies** in volunteers and subjects ranging in age from newborns to the elderly (N=1315) in which the test agent was **6% HES 130/0.4**, but also where test arm subjects received **2% or 4% HES 130/0.4** (exclusively studied in one sudden hearing loss trial among otherwise healthy subjects) and **10% HES 130/0.4**. The comparator was **HES 200** for most of these studies, **HES 450** for the single US-conducted study (**HS-13-30-US**), and normal saline, albumin or gelatin in the small number of remaining studies. Both single and multiple dose studies were performed, the latter lasting up to 28 days (see table 2 in text and tables 3 and 4 in APPENDIX).

Clinical Pharmacology

- ▶ In Phase 2 study **HS-13-12-DE**, isovolemic hemodilution using 500 mL 6% HES 130/0.4 versus 500 mL 6% HES 200/0.5 over 10-35 min was studied in subjects undergoing **preoperative autologous blood donation**. A total of 60 subjects were treated. Hemodynamic stability was equally well maintained in both treatment arms, and a safety analysis of hematology, clinical chemistry, AEs, and patient diaries showed no relevant differences between groups. Pruritus was more common in the 6% HES 130/0.4 than control group, but nausea was reported in 4 control subjects but 0 test subjects.
- ▶ The change in cardiac index after acute normovolemic hemodilution using 2000 mL of 6% HES 130/0.4 versus 6% HES 200/0.5 in subjects undergoing **major urologic surgery or Whipple procedure** was studied in **HS-13-18-BE**. Only 40 of a planned 60 subjects were enrolled and analyzed. There was no difference in the incidence of increased cardiac index or in the incidence of SAEs or AEs.
- ▶ Change in cardiac index in subjects undergoing **major cardiac surgery** was studied in **HS-13-21-DE**. Subjects received 10 mL/kg of either 6% HES 130/0.4 (N=10) or 6% HES 200/0.5 preoperatively as part of hypervolemic hemodilution. Both groups showed an increase in cardiac index (0.776 ± 0.373 versus 0.658 ± 0.551 , test versus control, respectively). Three test subjects and one control subject experienced a total of 7 SAEs.

Table 2: Clinical Study Roster (Source: Sponsor)

Study Subgroup (Phase)	Number of Subjects (%)		Indication
	6% HES 130/0.4	Control	
Phase I studies (N=67)			
DA277	12 (1.6)	-	Pharmacodynamics
HS-13-10-DE	24 (3.1)	-	Pharmacokinetics
HS-13-11-DE	12 (1.6)	-	Pharmacokinetics
HS-13-28-IDE	19 (2.5)	-	Pharmacokinetics in renally-impaired subjects
Volume replacement (N=705)			
HS-13-14-NL (III)	30 (3.9)	29 (5.3)	Cardiac surgery
HS-13-24-DE (II)	31 (4.0)	30 (5.5)	Cardiac surgery
HS-13-35-PL (II)	16 (2.1)	17 (3.1)	Cardiac surgery
HS-13-13-DE (III)	26 (3.4)	26 (4.8)	Orthopedic surgery
HS-13-19-FR (III)	52 (6.8)	48 (8.8)	Orthopedic surgery
HS-13-30-US (III)	49 (6.4)	51 (9.3)	Orthopedic surgery
HS-13-18-BE (II)	20 (2.6)	20 (3.7)	Urologic surgery
HS-13-27-DE (II)	41 (5.3)	41 (7.5)	Pediatric surgery
HS-13-36-FR (II)	32 (4.2)	33 (6.0)	Abdominal aortic surgery
HS-13-21-DE (II)	10 (1.3)	10 (1.8)	Acute hypervolemic hemodilution prior to cardiac surgery
HS-13-22-DE (II)	2 (0.3)	-	Severe sepsis subjects with acute pancreatitis or peritonitis
HS-13-25-CH (II)	16 (2.1)	15 (2.7)	Cranio-cerebral trauma
HS-13-12-DE (II)	30 (3.9)	30 (5.5)	Preoperative autologous blood donation
Sudden hearing loss (N=397)			
HS-13-16-DE (II)	98 (12.8)	89 (16.3)	Sudden hearing loss
HS-13-26-EU (II)	158 (20.6)	52 (9.5)	Sudden hearing loss
Stroke studies (N=146)			
HS-13-17-DE (II)	70 (9.1)	36 (6.6)	Acute ischemic stroke
HS-13-23-DE (II)	20 (2.6)	20 (3.7)	Acute ischemic stroke

2.2 Demographics

Sites

Studies were performed in Germany, Netherlands, Belgium, France, Switzerland, Austria, Czech Republic, Romania, Poland, and the US.

Ethnicity

74.4% (N=978) were Caucasian, 0.9% were defined as "other", whereas there are no data for the remaining 24.7%.

Gender

62% of subjects were males.

Age

The 18-64 year cohort was the largest (N=846). For the European studies, mean age for 6% HES 130/0.4 subjects was $48.8 \text{ years} \pm 12.0$ vs. 48.7 ± 11.9 years in controls. For the US study (HS-13-30-US), mean age was 49.2 ± 11.4 years in HES 130/0.4 subjects and 48.4 ± 11.9 years in HES 450 controls. Weight, height, and BMI were comparable as well.

A total of 386 subjects > 65 years (29%) were enrolled, 10% of whom had a serum creatinine > ULN. Although height, weight and BMI were comparable in the European studies in the 65-75 year old subgroup (N=298), all three parameters were higher in the US study because of a higher proportion of enrolled males. Subjects >75 years (N=88) also were studied. Mean age in the 6% HES 130/0.4 cohort was 78.9 ± 3.1 years vs. 79.4 ± 4.2 and 79.5 ± 5.6 years for subjects in the HES 200 and HES 450 cohorts, respectively.

Subjects <2 years (N=82) undergoing major abdominal, cranial, thoracic, or urological surgery were randomized to 6% HES 130/0.4 vs. 5% human albumin in a Phase 2 volume-replacement safety trial. Mean age was 0.3 ± 0.4 years and 0.2 ± 0.4 years in test and control arms, respectively.

PMH and Concomitant Disease

Since the Phase 1 trials were conducted in healthy volunteers, only 1267/1315 subjects were analyzed.

The most frequent MedDRA System Organ Class categories were for cardiac disorders (hypertension and coronary artery disease), musculoskeletal and connective tissue disorders (e.g., osteoarthritis), surgical and medical procedures, and vascular disorders (e.g., aortic aneurysm). A PMH of **renal and urinary disorders** was relatively uncommon. No subjects with **liver failure** or **dialysis-dependency** were treated.

See tables 1 and 2 in APPENDIX.

2.3 Dosing

Ceiling dose

In early European studies of 6% HES 130/0.4, adherence to the labeled ceiling dose of **33 mL/kg** was maintained. However, based on results from volume-replacement study **HS-13-24-DE**, the approved maximum dose in Europe was raised to **50 mL/kg** (vs. a labeled ceiling of **20 mL/kg** for HES 450/0.7 in the US).

Dose/kg

For the 6% HES 130/0.4 cohort, **27%** of enrolled subjects received **>40 mL/kg**, followed in descending order by the ≤ 10 mL/kg cohort (23.4%), >20-30 mL/kg (18.9%), >10-20 mL/kg (15.9%), and >30-40 mL/kg (14%).

For *all* HES 130/0.4 concentrations studied, **50.3% vs. 37.9%** (test vs. control, respectively) of subjects received **>40 mL/kg**, i.e., high dose exposure was more frequent for subjects receiving *any* 6% HES 130 product than for subjects receiving *any* type of control solution.

Total volume

The prescribed maximum daily dose for HES 130 was **33-70 mL/kg**, depending on the study.

For 6% HES 130/0.4, stratifying by absolute dose cohorts found that the largest dose subgroup (34.6% of test subjects) received ≤ 1000 mL, followed in descending order by the >1000-2000 mL cohort (24.2%), >2000-3000 mL cohort (16.3%), and the >4000 mL cohort (18.5%). Similar distribution was reported for HES 200 subjects, but corresponding dose cohorts for HES 450 subjects were ≤ 1000 mL (37.3%) and >1000-2000 mL (43.1%).

See tables 5 and 6 in APPENDIX.

2.4 Duration of exposure

For 6% HES 130/0.4 vs. control, the median number of treatment days, total volume of study solution and total volume of study solution/kg were *higher* in the test arm than in controls.

For 6% HES 130/0.4 vs. 6% HES 200, the median number of treatment days and daily volume of study solution were *similar*.

For 6% HES 130/0.4 vs. 6% HES 450, median number of treatment days was comparable, whereas duration of exposure, total volume of study solution and total volume of study solution/kg were *higher* in the test arm (since hetastarch ceiling is 1500 mL/kg).

2.5 Phase 1/2 studies

In Phase 1, 6% HES 130/0.4 was administered as a single dose (**HS-13-10-DE** and **HS-13-28-DE**), as multiple doses for 10 consecutive days (**HS-13-11-DE**), or in 2 consecutive periods (**DA277**). One Phase 1 study investigating the effect of 6% HES 130/0.4 on blood and plasma volume using radiolabeled erythrocytes was conducted in healthy volunteers.

Three double-blind, controlled (6% HES 200/0.5) Phase 2 clinical trials also were conducted using surrogate endpoints of plasma volume expansion, i.e., BP, cardiac index, and cardiac filling pressures. The endpoint in these trials was the amount of HES solution required to restore or maintain plasma volume expansion.

2.6 Phase 3 studies

Four Phase 3 trials were conducted, three of which were in Europe using 6% HES 200/0.5 as control and one in the U.S. using 6% HES 450/0.7 as control. See table 7 in APPENDIX.

Exclusion criteria for the European trials included a history of **heart, kidney, liver**, diabetes, or severe infectious diseases, history of coagulation disorders, known allergy to starch, BW >100 kg, pregnancy, and lactation. In the single US volume replacement study (**HS-13-30-US**), exclusion criteria included previous cardiac surgery, anemia, pancreatitis, known allergy to HES, **renal and hepatic disorders**, pregnancy, and lactation.

- **HS-13-13-DE** was an RCT for volume replacement therapy conducted in subjects (N=52) undergoing major **orthopedic surgery** that compared perioperative volume replacement using **6% HES 130/0.4 vs. 6% HES 200/0.5**.
- **HS-13-19-FR** was a confirmatory volume replacement RCT of **HS-13-13-DE** that compared **6% HES 130/0.4 vs. 6% HES 200/0.5** in 100 subjects undergoing **orthopedic surgery**.
- **HS-13-14-NL** was a double-blind, volume-replacement RCT in 2 centers designed to show equivalency in perioperative volume management in subjects undergoing **cardiac surgery**.
- **HS-13-30-US** was a multicenter, double-blind, pivotal volume replacement RCT in subjects undergoing **orthopedic surgery** designed to show equivalency of **6% HES 130/0.4** with **HES 450/0.7**.

2.7 Exposure in selected populations

Non-dialysis-dependent renal impairment

HS-13-28-DE: this was a single-dose, open-label, non-randomized, single-center **pK study of non-dialysis-dependent** renally impaired subjects (N=19) stratified by creatinine clearance: 15 to <30 (N=6), 30 to <50 (N=4), 50 to <80 (N=5), and 80 to <120 mL/min (N=4).

Subjects received **one** intravenous infusion of 500 mL 6% HES 130/0.4 over 30 min. Blood samples were collected prior to start of infusion and up to 72 hr after start of infusion for analysis of plasma HES concentration. Urine samples were collected prior to start of infusion and up to 72 h/96 h after start of infusion to analyze the amount of HES excreted.

Results: $AUC_{(0-inf)}$ in subjects with $CCr < 50$ mL/min was, on average, 73% greater than in subjects with $CCr \geq 50$ mL/min, and greater still in the 15 to < 30 mL/min cohort compared to the 30 to < 50 mL/min cohort. $AUC_{(0-inf)}$ and total plasma clearance clearly depended on renal function ($r = -0.76$, $p < 0.001$), a relationship that was stronger when age and BMI were controlled for ($r^2 = -0.89$). Alpha elimination half-life was prolonged to **0.6 h** in subjects with CCr between 80 to 120 mL/min, compared to about **1.5 h** in subjects with $CCr < 50$ mL/min. C_{max} and beta elimination half-life (**16.1 h**, range: 14.1-18.9 h) were not affected by renal impairment.

Conclusion: Severe **non-dialysis-dependent renal failure** ($CCr < 50$ mL/min) increases HES plasma levels, resembling the pK profile of HES 200/0.5 in healthy volunteers. Although major accumulation is not expected, (according to the sponsor), an adjusted dosing schedule may be required for subjects with $CCr < 50$ mL/min. The $AUC_{(0-inf)}$ changes in subjects with $CCr \geq 50$ mL/min are probably not clinically relevant.

Severe sepsis

HS-13-22-DE: this controlled (crystalloid) Phase 2 volume-replacement trial studied 6% HES 130/0.4 for initial volume stabilization and effect on EVLW in subjects with severe sepsis. **THE STUDY WAS STOPPED FOR SLOW ENROLLMENT.**

Cardiac surgery

HS-13-14-NL was a randomized, controlled, double-blind Phase 3 **supportive** volume-replacement trial in 2 centers designed to show equivalency between 6% HES 130/0.4 and 6% HES 200/0.5 in perioperative volume management for subjects undergoing elective CABG surgery.

Perioperative volume management included ANH prior to bypass with 500 mL of test or control solution, pre-bypass volume replacement with test or control solution according to the subject's clinical status, priming of the pump with 1000 mL of test or control solution, and post-bypass volume replacement with the test or control

solution. After reaching the dose limit of 3000 mL of test or control solution, the investigator switched to human plasma protein solution. The primary endpoint was volume of total colloids infused until 16 h postoperatively. A total of 59 subjects were treated with either 6% HES 130/0.4 (N=30) or 6% HES 200/0.5 (N=29).

Results

The volume of test solution infused was no different from control solution: 2913 ± 779 mL versus 2884 ± 1175 mL, respectively. Expressed in terms of body weight, these results were **31.0 mL/kg versus 30.6 mL/kg**, respectively. The 95% confidence interval for the difference was (-488 mL, 535 mL), slightly wider than the prespecified interval was (-500 mL, 500 mL), so **equivalence could not be demonstrated**, although a 35 mL difference is not clinically meaningful. The volume of crystalloid given was comparable, indicating crystalloids were not used to compensate for colloid volume. A total of 16 test subjects and 11 control subjects received the maximum study medication dose of 3000 mL.

SAEs were observed in 3 test subjects (1 case of cerebral infarction, 2 cases of heart failure) and 2 control subjects (bleeding in one subject, and hypotension, atrial fibrillation, ischemia, bleeding, and clotting disorder in the other subject). The most noticeable difference was a larger decrease in platelet count in the HES 200 arm. Test subjects had a greater increase in factor VIII antigen and vWF, which reached significance at the end of the investigational period.

HS-13-24-DE: this randomized, non-inferiority Phase 2 volume-replacement trial using 6% HES 200/0.5 up to its daily limit of **33 mL/kg** studied blood loss after **high dose** infusion (mean: **48 mL/kg**) of 6% HES 130/0.4. Continuation solution for both groups was 3.5% gelatin. Non-inferiority was predefined as estimated blood loss (EBL) test solution > control solution by ≤ 600 mL.

Results

Mean blood loss was 2339 mL versus 2724 mL, test versus control arm, respectively, i.e., **non-inferiority was demonstrated**. The mean volume of allogeneic RBCs transfused was 290 versus 392 mL, respectively. There were no significant between-group differences with respect to platelet count, fibrinogen concentrations, or other coagulation parameters, even though considerably more 6% HES 130/0.4 was infused than control solution. Curiously, vWF and ristocetin cofactor did not decline during the study period. In fact, vWF *increased* 48 h after start of the infusion and ristocetin cofactor *increased* after 33 mL/kg of colloid in both treatment groups. SAEs

were reported in 9 test subjects versus 8 control subjects. One control subject died.

HS-13-35-PL: this controlled (3% gelatin, N=17)), randomized, open-label, Phase 2 volume-replacement trial studied 6% HES 130/0.4 (N=16) in subjects undergoing elective CABG surgery, from induction of anesthesia to POD 1, including priming of the bypass machine with 500 mL of colloid and 1000 mL of crystalloid. The primary endpoint was volume of colloid needed to restore or maintain hemodynamics in the perioperative period. Subject demographics were comparable between groups, whereas bypass time, cross-clamp time, and duration of ventilation were longer in the test arm.

Neither the volume of colloid infused between groups (1719 vs. 1853 mL), hemodynamics, platelet counts, platelet function, INR, PTT, ACT nor EBL were different between groups.

Three SAEs occurred, one in the test arm and two in the control arm.

Severe TBI

HS-13-25-CH: this controlled (6% HES 200/0.5 up to the labeled ceiling dose of 33 mL/kg), randomized, open-label, single-center, Phase 2 volume-replacement trial compared bleeding complications, coagulation interventions, and coagulation parameters in subjects with severe TBI after daily, repetitive, high dose (up to 70 mL/kg) infusion of 6% HES 130/0.4 followed by 5% albumin. If more colloid than 70 mL/Kg/day was required, FFP was used in both groups.

For most coagulation parameters and time points, there were no between-group differences. Factor VIII activity was significantly higher on Day 4 with test solution. Higher values were also observed for vWF on Days 4 and 6. Ristocetin cofactor activity was higher on Day 2 and Day 6 in test subjects. Overall, no impairment of coagulation was observed despite very high doses of 6% HES 130/0.4.

A total of 40 (N=20 in each arm) subjects were planned, but after 31 subjects (N=16 versus 15) had been enrolled, the IRB conducted an interim analysis and recommended halting the study because of ICP increases observed in the control arm: the number of subjects with ICP increases ≥ 35 mmHg was 3/16 vs. 12/15. Mortality was 4/16 versus 3/15. Preliminary results also showed that the incidence of intracranial bleeding (5 episodes in each arm) and coagulation interventions (defined as reaching predefined laboratory triggers) were not different between groups. The number of colloid treatment days was shorter in the test arm (6.6 versus 11.8 days) but total HES

volumes were not significantly different. The number of ventilator days was 9.6 vs. versus 15.6 and the number of ICU days was 12.7 vs. 19.5. Two control arm subjects dropped out of the study because of renal failure. In the remaining subjects, Cl_{Cr} and mean SCr remained WNL during the entire study.

Abdominal aortic aneurysm surgery

HS-13-36-FR: this controlled (3% gelatin, N=33), randomized, open-label, multicenter, Phase 2 volume-replacement trial studied 6% HES 130/0.4 (N=32) with respect to **postoperative renal function** in subjects undergoing aortic surgery with a pre-operative $CCr \leq 80$ mL/min (Cockcroft formula) who were ≥ 18 years of age. Mean amount of total colloids infused was 1960 mL for test arm subjects and 1928 mL for control subjects. Equivalent volumes in terms of mL/kg were 24.2 and 24.5 mL/kg.

PTT at 4-6 h post-surgery and thrombin time at the end of surgery *decreased* slightly in the test group but *increased* in the control group. Differences in PTT overall were significant by ANOVA ($p < 0.05$). Factor VIII concentration showed a significantly greater increase in test subjects than control subjects at 4-6 h post-surgery.

Three test subjects and two control subjects were prematurely withdrawn from the study. CTM was administered for volume replacement according to the anesthetist's clinical judgment. The primary endpoint, peak increase in Cl_{Cr} from baseline to POD 6 or D/C, was slightly higher in control subjects (26.3 versus 36.5 $\mu\text{mol/l}$). A total of 8/32 test subjects versus 4/33 control subjects experienced SAEs. **The only SAE related to the renal system (dialysis-dependency) occurred in a control subject.** Two subjects in each treatment arm died during the study following SAEs. Postoperative renal dysfunction, minimum postoperative Cl_{Cr} , oliguria, and urinary NAG levels were no different between-groups. The pre-specified Δ for non-inferiority was not met until 2 outliers, one in each treatment arm, were excluded from the analysis.

Ischemic stroke

HS-13-17-DE: this controlled (normal saline), double-blind, randomized, multicenter, international, Phase 2 parallel group safety trial studied hypervolemic therapy in subjects with acute cerebral ischemia. Hypervolemic therapy was performed using a repetitive bolus infusion scheme. One bolus consisted of 250-500 mL study drug administered *tid* on days 1-3. On days 4-7, subjects received a single bolus infusion *qd*. Overall, 70 subjects were treated with 10%

HES130 and 36 with saline. The incidence of subjects experiencing ≥ 1 SAE was lower in the test group (27.8% versus 18.5%). Permanent discontinuation of study drug due to SAEs occurred in 2 test subjects versus 3 control subjects.

AEs were similar between-groups, with CV events the commonest AEs reported, especially arrhythmia: 21.4% versus 36.1%. Bleeding events occurred in only 2 subjects per group and there was a single allergic reaction in a test subject. In total, 4 test subjects vs. 3 control subjects died as a result of treatment-emergent SAEs during the study.

HS-13-23-DE: this controlled (crystalloid), double-blind, randomized, Phase 2 single-center trial studied the effect of hypervolemic therapy on cardiac output and cerebral blood flow using a continuous infusion scheme. Subjects received 6.5 L of study drug over 96 hrs, corresponding to an infusion rate of 62 mL/hr. Subjects (N=40) were randomized 1:1 to treatment. No difference in cardiac output or cerebral perfusion were noted between groups. The incidence of AEs was identical between groups, with pruritus reported most often as the AE (3 versus 2). No subject died.

Orthopedic Surgery

HS-13-13-DE was a supportive Phase 3 **volume-replacement** study conducted in subjects (N=52) undergoing major elective **orthopedic surgery** comparing perioperative volume replacement using 6% HES 130/0.4 vs. 6% HES 200/0.5.

CTM initially was infused until Hct $< 28\%$, at which time CTM (up to 3000 mL) + RBCs were infused 1:1. Further volume replacement at 1:1 continued up to 2000 mL of RBC, after which time RBC + FFP + platelets were administered 1:1:1. If the HES dose limit of 33 mL/kg was reached, the investigator switched to 5% albumin.

The primary endpoint was volume of HES + albumin infused until 4-6 hr after surgery. The decision to infuse was based on clinical judgment.

Results

Mean volumes of CTM infused were 2019 ± 556 mL vs. 2188 ± 1050 mL, test vs. control, respectively, equivalent to **25.4 mL/kg vs. 26.5 mL/kg**, respectively. Due to one outlier in the control group (subject #43) who received 6600 mL colloid solutions, the confidence interval (-637 mL, 299 mL) exceeded the prespecified range and **equivalence**

could not be demonstrated. The most frequent AEs in both groups were postoperative nausea and/or vomiting. No SAEs were observed. Favorable trends of 6% HES 130/0.4 compared to HES 200 were found for several coagulation parameters. Mean decreases of factor VIII antigen, vWF, ristocetin cofactor, and coagulation factor VIII were shorter-lasting and less pronounced in test arm subjects. For factor VIII antigen, vWF, and ristocetin cofactor at 4-6 h post-surgery, between-group differences were significant.

HS-13-19-FR was a confirmatory Phase 3 volume-replacement trial of HS-13-13-DE in 100 subjects undergoing elective **orthopedic surgery** (as opposed to 52 subjects in HS-13-19).

Volume replacement with 6% HES 130/0.4 vs. 6% HES 200 was performed up to a maximum of 33 mL/kg, after which volume replacement continued with any colloid other than HES. RBC were transfused if hematocrit decreased to < 25% and/or hemoglobin decreased to < 8 g/dL. Platelets were administered for intraoperative bleeding (clinical judgment) or if volume replacement exceeded 5000 mL.

The endpoint was equivalency for volume of total colloids (HES + colloids other than HES) infused until 4-6 h after surgery. Four centers enrolled 100 subjects, of which 52 were randomized to 6% HES 130/0.4 and 48 subjects to 6% HES 200/0.5. THR was performed in 26 test subjects and 26 control subjects, spinal surgery was done in 26 test subjects and 19 control subjects, and knee and femoral surgery were performed in 4 test subjects and 3 controls.

Results

Mean volume of total colloids was 1960 mL \pm 971 in the test arm and 1928 \pm 901 mL in controls. The 95% confidence interval for the difference was (-330 mL, 284 mL), which was less than the prospectively defined confidence interval (-500 mL, 500 mL). Net fluid output was greater for control subjects than test subjects (4039 mL versus 3597 mL), whereas urine output was slightly higher in the test group.

Four SAEs were reported: pulmonary edema, hypovolemia due to major bleeding, and severe hypotension in the test arm and MI in the the control arm arm. In the opinion of the investigator, relationship to drug was “probable” for postoperative hemorrhage, and “possible” for pulmonary edema and hypovolemia due to bleeding. The test arm MI was “unlikely” or “not assessable”.

Factor VIII concentration showed a significantly larger mean increase with test product than control. PTT was significantly prolonged in the

control arm compared to test arm. Mean increase in α -amylase was lower in test arm subjects.

HS-13-30-US was a controlled, randomized, double-blind, multicenter pivotal Phase 3 volume-replacement trial in subjects ≥ 18 years of age undergoing **elective orthopedic surgery** with an expected blood loss ≥ 500 mL. It was designed to show equivalency of **6% HES 130/0.4 with HES 450/0.7**.

The primary endpoint was **“total volume of colloid solution required for intraoperative volume replacement until end of surgery”**. Secondary efficacy endpoints were total fluid input and output, and use of vasoactive medications. Primary safety endpoints included calculated total perioperative EBL (induction of anesthesia to 48 h after end of surgery), nadir factor VIII activity, nadir vWF antigen concentration within 2 h of completion of surgery, and use of FFP. **Per amendment 5 (8 JUN 2002), the sponsor proposed to control the type 1 error rate by conducting safety analyses sequentially.** Accordingly, if EBL was not significant, tests for factor VIII activity, vWF antigen and FFP administered would be considered **exploratory**. Secondary safety endpoints included SBP $\leq 30\%$ below the value immediately before induction of anesthesia, and AEs including bleeding and abnormal laboratory indices of hemostasis, serum chemistry, and urine analysis.

In addition to the ITT analysis (N=49 vs. 51, test vs. control, respectively), 3 subgroups were defined *a priori*:

- Subset 1: subjects hemodynamically stable at the end of surgery, both at end of wound closure and immediately after arrival in the recovery room (N=48 vs. 51)
- Subset 2: subjects with ≤ 25 mL/kg blood loss and without use of colloids other than 6% HES 130/0.4 or HES 450/0.7 (N=45 vs. 44)
- Subset 3: subjects who received >1000 mL 6% HES 130/0.4 or HES 450/0.7 (N=35 vs. 32)

EBL was calculated as:

$$EBV * (Hct_{screening} - Hct_{POD2}) + \text{transfused RBC volume}$$

where transfused RBC volume was estimated as:

$$0.7 * \text{infused RBC} + 0.6 * \text{infused salvaged RBC} + 0.35 * \text{infused whole blood}$$

Subjects with known hypersensitivity to HES, coagulation disorders, anuria or oliguria (defined as urine output <500 mL/day), NYHA class III or IV, unstable angina or pregnancy were excluded from enrollment. Infusion was titrated against CVP, which was monitored in all subjects (table 3). No study or other colloids were administered *before* induction of anesthesia or within 2 h *after* end of surgery. Electrolyte solutions were infused at 7 mL/kg before and during induction of anesthesia until end of surgery. (This end-of-surgery timepoint differed from the remaining Phase 3 trials where treatment extended into the postoperative period, but no additional colloids were needed during this period.)

Measurements of PT, PTT, Fb, VIII, and vWF were performed immediately after induction of anesthesia, at the end of surgery, and at 2, 24, and 48 h after surgery. Safety was evaluated through Day 28.

Table 3: Treatment Algorithm for Study HS-13-30-US		
	BP Acceptable	BP Unacceptably Low
CVP <10 mmHg	Infuse colloid	Infuse colloid
CVP 10-15 mmHg	No Rx	Infuse colloid or vasoactive drugs
CVP >15 mmHg	No Rx	Use vasoactive drugs

Results

A total of 100 subjects were enrolled in the trial (ITT analysis: N=49 vs. 51), most of whom underwent elective surgery of the spine or hip.

Primary endpoint

The ratio of 6% HES 130/0.4 to HES 450/0.7 infused was 1.024 (95% confidence interval: 0.83, 1.254), well **within the prospectively defined equivalence range** of (0.55, 1.82). Mean volume of colloid infused was 1613 ± 778 mL vs. 1584 ± 958 mL (equivalent to 18.0 mL/kg vs. 19.6 mL/kg, respectively), with more than 60% of subjects in each group receiving >1000 mL. Median volume of CTM administered was 1500 mL in both groups. A total of 8 subjects received >3000 mL of clinical trial material (subgroup 3): 3 test subjects and 5 control subjects.

Volumes of HES infused did not differ significantly between any of the subgroups. There were no between-group differences in the amount of crystalloid administered intraoperatively, and there were no significant differences in CVP values, hemodynamics, mean fluid input, urine output, or vasoactive drug therapy between groups. Only 4 subjects in each treatment arm received FFP.

AEs

No subject died during the study and no differences were observed in the frequency of AEs. In terms of SAEs, a total of 5 test subjects reported 7 events vs. 9 subjects who reported 11 events. For all SAEs in the test arm, an “unlikely” relationship was attributed. In terms of severe intensity events, 10 test subjects experienced 11 events vs. 11 control subjects who experienced 18 events.

Non-serious bleeding events were observed in 7 test subjects (14.3%) vs. 9 control subjects (17.6%), but **serious coagulopathies** occurred in 3 control subjects vs. no test subjects. **In these 3 cases, >3000 mL of HES 450/0.7 was administered**, for which attribution was “possibly related”. “Possibly related” events included prolonged PTT and PT, wound hemorrhage, anemia and pruritus for 6% HES 130/0.4 and coagulopathy and pruritus for HES 450.

Transfusion

The number of allogeneic RBC units transfused was not different between-groups. However, between-group differences were apparent when total **allogeneic RBC + salvaged blood** in mL/kg body weight was calculated for the ITT population (8.0 ± 6.4 mL/kg vs. 13.8 ± 12.9 mL/kg; $p=0.03$, *exploratory*) and for subgroup 3 (8.6 ± 7.0 mL/kg vs. 16.5 ± 13.6 mL/kg; $p=0.04$, *exploratory*). It should be noted that these analyses were *post hoc*. See tables 4 and 5, below.

Platelet count

Platelet counts were not different between-groups.

Factor VIII

Factor VIII activity decreased in *both* treatment groups at the end of surgery. Thereafter, values increased disproportionately more in test arm subjects than in control arm subjects. At 2 h post-surgery, differences between treatment groups were not statistically different, but at 24 and 48 h post-surgery, Factor VIII values were *higher* in test arm subjects than control subjects ($p<0.001$, t-test) based on change from baseline. Fewer subjects given the test article had factor VIII activity below the lower limit of normal at the end of surgery (5 vs.

13; $p=0.03$, *exploratory*) and at 2 h post-surgery (0 vs. 7; $p=0.03$, *exploratory*).

vWF (Ristocetin)

vWF levels decreased in *both* treatment groups at the end of surgery. Thereafter, values increased disproportionately more in test arm subjects than in control arm subjects. At 2 h post-surgery ($p<0.05$, *exploratory*) and at 24 h and 48 h post-surgery ($p<0.001$, *exploratory*), vWF values were *higher* than control values based on change from baseline. *Fewer* ($p=0.03$, *exploratory*) test subjects (0 vs. 4) had abnormally decreased vWF levels. At 24 and 48 h, values for vWF antigen were substantially *higher* ($p<0.0001$, *exploratory*) in test arm subjects.

Table 4: Results for 4 Primary Safety Variables in HS-13-30-US (Source: Sponsor)

Variable	Mean		Ratio 6% HES 130/0.4 / HES 450	
	6% HES 130/0.4	HES 450	Estimate	95% CI
EBL (mL)	1.17	1.31	0.910	0.720, 1.141
Factor VIII (%)*	100.5	81.4	1.244	1.000, 1.563
vWF (%)*	97.7	88.7	1.128	0.991, 1.285
FFP (mL)*	72	144	0.723	0.000, 2.437

Per protocol, these analyses were exploratory since EBL was not statistically significant at $p=0.05$

Table 5: Changes in Coagulation Values from HS-1330-US (Source: Sponsor)			
Parameter & Timepoint	6% HES 130/0.4 N=49	HES 450 N=51	6% HES 130/0.4 — HES450 Point estimate (95% CI)
Platelets (x 10⁹/L)			
Immediately post-induction	206 ± 74	203 ± 60	
End of surgery	-28 ± 47%	-39% ± 48%	9.9 (-5.8, 25.6)
2 h post surgery	MD	MD	MD
24 h post surgery	MD	MD	MD
48 h post surgery	-37 ± 64%	-43 ± 49%	4.4 (-13.3, 22.1)
PTT (sec)			
Immediately post-induction	29 ± 5	28 ± 4	
End of surgery	4.2 ± 7%	6 ± 7%	-2.3 (-5.1, 0.6)
2 h post surgery	0.2 ± 6%	3 ± 6%	-3.0 (-5.2, -0.8)
24 h post surgery	0.8 ± 6%	6 ± 7%	-5.0 (-7.7, -2.3)
48 h post surgery	1.3 ± 7%	5 ± 6%	-3.0 (-5.1, -0.8)
VIII			
Immediately post-induction	146 ± 62	143 ± 71	
End of surgery	-48 ± 50%	-54 ± 70%	12.2 (-7.2, 31.5)
2 h post surgery	12 ± 94%	-16 ± 89%	31.2 (-3.1, 65.4)
24 h post surgery	96 ± 96%	8 ± 68%	94.6 (62.7, 126.5)
48 h post surgery	172 ± 86%	81 ± 79%	97.1 (65.0, 129.2)
VWF			
Immediately post-induction	133 ± 55	135 ± 55	
End of surgery	-33.5 ± 36%	-39 ± 45%	7.4 (-5.9, 20.9)
2 h post surgery	2 ± 57%	-25 ± 54%	25.7 (6.5, 44.9)
24 h post surgery	89 ± 51%	14 ± 56%	78.4 (59.8, 96.9)
48 h post surgery	127 ± 45%	74 ± 55%	54.0 (34.8, 73.3)

Subgroup 3

In subgroup 3, factor VIII activity was *higher* in the 6% HES 130/0.4 arm (89%) than in the HES 450/0.7 arm (66%). Nadir vWF Ag concentration within 2 h post-surgery was *higher* ($p=0.008$) in the 6% HES 130/0.4 arm (89% of baseline) than in the HES 450/0.7 arm (72%).

PT and PTT

Mean PTT and PT increased slightly from baseline until the end of surgery in both treatment groups and were only marginally increased for 6% HES 130/0.4 at later time points, but remained slightly increased for controls. Confidence intervals for PTT and PT values were *lower* in test arm subjects at 24 h ($p=0.004$ and $p<0.0001$, respectively) and at 48 h ($p=0.007$ and $p=0.0033$, respectively) after surgery.

Amylase

α -amylase was lower ($p<0.05$) in test arm subjects at 48 h (125 ± 91 vs. 65 ± 48 U/l).

Serum creatinine

All subjects had serum creatinine measured just after induction of anesthesia, at the end of surgery, and at 48 h post-surgery. Two study time data points were missing for 1 test subject and one study time data point was missing for 6 test and 8 control subjects.

Review of the available data shows that only 3/100 subjects had elevated SCr at any time. These included 2 test subjects and 1 control subject:

- Subject #58: received 1000 mL 6% HES 130/0.4 (SCr of 1.2, 1.3, and 1.5 at post-anesthetic induction, end of surgery, and 48 h post-surgery, respectively)
- Subject #60: received 3000 mL of 6% HES 130/0.4 (SCr of 2.5, 2.4, and 3.3)
- Subject #36: received 1500 HES 450 (SCr 1.9, 1.7, and 2.7)


LFTs

ALT (SGPT) is considered to be the most specific LFT for liver injury and was captured at 3 times during the trial: immediately after induction of anesthesia, end of surgery, and 48 hours after

end of surgery. For the purposes of this review, an exploratory analysis of ALT levels was undertaken.

Of the 100 subjects, 7 subjects (5 test subjects and 2 control subjects) experienced treatment-emergent ALT elevations (see table, below). None of the elevations was clinically significant.

See table 6, below.



Conclusion

6% HES 130/0.4 was equivalent to control in terms of volume replacement but had a better safety profile in terms of bleeding events and coagulation parameters. The ALT and SCr profiles were similar between-groups.

Pediatrics

HS-13-27-DE: this controlled (5% human albumin) Phase 2 volume-replacement safety trial studied 6% HES 130/0.4 in pediatric subjects (newborn, infants) undergoing major abdominal, cranial, thoracic, or urological surgery. A total of **82 subjects** were randomized and treated, 41 in each treatment arm. Mean age was 0.3 ± 0.4 years and 0.2 ± 0.4 years in test and control arms, respectively. One control subject died before completion of the study, and all other subjects completed the study.

Total dose (mean) to 4-6 h postoperatively was **16.0 mL/kg** in the test arm and **16.9 mL/kg** in the control arm. From 4-6 h postoperatively to POD 1, it was 0.9 mL/kg vs. 2.5 mL/kg, respectively. Overall, no specific effect on hemostasis was observed in test subjects. Mean PTT values showed no change in the test arm (37.0 sec at baseline and 37.1 sec at POD 1) vs. a trivial increase for the albumin group (38.2 sec at baseline and 39.6 sec at POD 1). Mean platelet values decreased in both treatment arms, from 397 at baseline to 313 at POD 1 in the test arm (79% of baseline) and from 414 to 348 in the albumin arm (84% of baseline).

One subject in the control arm died as a result of an SAE, attribution of which was not made. In total, five (6.1%) subjects experienced at least one treatment-emergent SAE during the study, three (7.3%) subjects in the 6% HES 130/0.4 arm and two (4.9%) subjects in the control arm. There were no major differences in the frequency of AEs between test product (80.5%) and albumin (78.0%). Hemodynamics were not different between treatment arms.

Sudden hearing loss

HS-13-16-DE: this controlled (6% HES 200/0.5), randomized, double-blind, multicenter, Phase 3 trial studied the hemodilution effect of using 10% HES 130/0.4 **every day for 10 days** in subjects with sudden hearing loss. After enrollment of 187 subjects, an interim analysis showed that mean absolute hearing gain was 17 dB in the test arm and 19.5 dB in the control arm. Pruritus was more frequent and longer-lasting in the 10% HES 130 arm (19%) than in the HES 200 arm (8%). All other AEs were comparable in both groups and there were no major differences in changes in clinical laboratory parameters. The study was halted prematurely after the sponsor ceased development of the 10% HES 130/0.4 product.

HS-13-26-EU: this controlled (5% glucose), randomized, double-blind, Phase 2 multicenter trial studied different doses for **6-day therapy** of sudden hearing loss. Although no differences in hearing gain were noted, pruritus was clearly more frequent in the test groups (6%, 4%, and 2% HES 130/0.4). One SAE occurred in the control arm and in each treatment subgroup. Of note, one of these events was an anaphylactic reaction.

3.0 SAFETY

To strengthen the robustness of the analysis, the sponsor compared the safety profile for subjects in the **HES 130 total arm** (N=768), including included 471 subjects in the **HES 130/0.4 arm** (N=471), against subjects in the **Control totals arm** (N=547; HES 200, HES 450, normal saline, crystalloids, glucose, albumin, and gelatin), including 51 subjects in the **HES 450 arm** (N=51).

Table 7 summarizes the safety profile of the product. It shows that in the aggregate, 6% HES 130/0.4 is no different from other HES 130/04 solutions or from control solutions (HES 200, HES 450, primarily).

The following should be noted with respect to the safety analysis:

- The HES 450 cohort was an order of magnitude smaller than the other treatment arms. Hence, the reliability of incidence reports is less certain than for larger cohorts.
- The incidence of AEs across studies should not be given equal weight because study populations with diverse comorbidities at baseline were studied, e.g., subjects who had experienced stroke.
- In some case, larger volumes of 6% HES 130/0.4 than control solutions, e.g., HES 450, were administered.

Table 7: Summary of Safety (Source: Sponsor)			
Category	6% HES 130 (N=471)	HES 130 Total (N=768)	Controls (N=547)
Any AE	271 (57.5)	413 (53.8)	312 (57.0)
Any AE leading to death	6 (1.3)	11 (1.4)	10 (1.8)
Any AE leading to withdrawal from study	5 (1.1)	16 (2.1)	10 (1.8)
Any related AE	79 (16.8)	156 (20.3)	110 (20.1)
Any SAE (excluding death)	38 (8.1)	50 (6.5)	43 (7.9)
Any severe intensity AE	42 (8.9)	67 (8.7)	58 (10.6)

3.1 Deaths

For studies in which death occurred, the aggregate mortality was 2.8% vs. 3.9%, HES 130 total vs. control total, respectively.

For non-stroke volume replacement studies in which death occurred, mortality was 1.3% vs. 2.9%. For the two stroke studies (HE-13-17-DE and HE-13-23-DE; N=146), mortality was 3.4% with 10% HES 130 vs. 2.1% with normal saline.

See table 8, below, and narratives.

Table 8: Mortality (%) in Studies Where Death Occurred (Source: Sponsor)					
Study	Population	Test Solutions		Control Solutions	
		6% HES 130/0.4	10% HES 130/0.4	HES 200	Non-HES Solutions
<u>Stroke studies</u>					
HS-13-17-DE (N=106)	Stroke		5 (5.0)		3 (3.0)
HS-13-23-DE (N=40)	Stroke		0		0
Stroke Subtotal (N=146)			5 (3.4)		3 (2.1)
<u>Non-stroke studies</u>					
HS-13-24-DE (N=61)	CABG			1 (2.0)	
HS-13-25-CH (N=33)	TBI	4 (1.2)			3 (0.9)
HS-13-27-DE (N=82)	Ped surgery				1 (1)
HS-13-36-FR (N=65)	AAA surgery	2 (3.1)			2 (3.1)
Non-stroke Subtotal (N=241)		6 (1.3)			7 (2.9)
Total Mortality (N=387)		11 (2.8)		10 (3.9)	

3.2 SAEs

The incidence of "any SAE" and coagulopathy were noticeably higher in the HES 450 treatment arm. See table 9.

Table 9: Serious Adverse Events by Treatment Group (Source: Sponsor)				
System	Test Solutions		Control Solutions	
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Any SAE	10 (4.9)	50 (6.5)	8 (15.7)	43 (7.9)
Blood & lymphatic	0	1 (0.1)	3 (5.9)	4 (0.7)
Coagulopathy	0	0	3 (5.9)	4 (0.7)
Cardiac disorders	13 (2.8)	19 (2.5)	0	8 (1.5)
Myocardial infarction	5 (1.1)	5 (0.7)	0	2 (0.4)
Heart failure	3 (0.6)	4 (0.5)	0	2 (0.4)
Atrial fibrillation	1 (0.2)	1 (0.1)	0	1 (0.2)
GI disorders	2 (0.4)	2 (0.3)	0	2 (0.4)
Anaphylactic reaction	1 (0.2)	2 (0.3)	0	0
Nervous system disorders	5 (1.1)	8 (1.0)	1 (2.0)	15 (2.7)
Respiratory system disorders	5 (1.1)	6 (0.8)	2 (3.9)	6 (1.1)
Vascular disorders	6 (1.3)	8 (1.0)	0	7 (1.3)
Hemorrhage	0	0	0	4 (0.7)

3.3 Adverse events of severe intensity

Similar frequency across treatment arms except for a noticeably higher incidence of severe intensity AEs in the HES 450 treatment arm. See table 10.

Table 10: AEs of Severe Intensity by Treatment Group (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Any AE	42 (8.9)	67 (8.7)	11 (21.6)	58 (10.6)
Blood & lymphatic disorders	3 (0.6)*	3 (0.6)	3 (5.9)	4 (0.7)
Cardiac disorders	10 (2.1)	13 (1.7)	0	10 (1.8)
Procedural complications	9 (1.9)	10 (1.3)	2 (3.9)	5 (0.9)
Nervous system disorders	1 (0.5)	1 (0.5)	2 (3.9)	15 (2.7)
Respiratory disorders	5 (1.1)	8 (1.0)	2 (3.9)	6 (1.1)
Vascular disorders	4 (0.8)	6 (0.8)	0	15 (2.7)

*HES 130/0.4 treatment arm: 2 subjects with postoperative bleeding and one with intraabdominal hemorrhage were reported as "possibly related"

3.4 Common adverse events (defined as >5% incidence in the HES total treatment arm)

Similar incidence across groups except for increased nausea (43.1%) and pruritus in the HES 450 treatment arm. See table 11.

Table 11: Common (>5%) Adverse Events by Treatment Group (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Nausea	42 (8.9)	51 (6.6)	22 (43.1)	48 (8.8)
Pruritus	23 (4.9)	49 (6.4)	5 (9.8)	24 (4.4)
Constipation	37 (7.9)	46 (6.0)	22 (4.3)	33 (6.0)
Headache	17 (3.6)	45 (5.9)	3 (5.9)	19 (3.5)

3.5 Uncommon adverse events (defined as 1- 5% incidence)

Similar frequency across groups except for increased incidence of vomiting in the HES 450 treatment arm. See table 12.

Table 12: Uncommon (1- 5%) Adverse Events by Treatment Group (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Vomiting	26 (5.5)	31 (4.0)	9 (17.6)	33 (6.0)
Amylase increased	5 (1.1)	12 (1.6)	0	12 (2.2)
Atrial fibrillation	7 (1.5)	10 (1.3)	1 (2.0)	21 (3.8)
Post procedural bleeding	10 (2.1)	10 (1.3)	0	11 (2.0)

3.6 AEs in Subgroups

Pediatric subjects

Similar frequency across groups except for increased incidence of blood & lymphatic disorders and cardiac disorders in the albumin treatment arms. See table 13.

Table 13: AEs in Subjects <2 y (Source: Sponsor)				
	6% HES 130/0.4 N=41 (%)	HES 130 Total N=41 (%)	Albumin N=41 (%)	All Controls N=41 (%)
Any AE	33 (81)	33 (81)	32 (78)	32 (78)
Blood & lymphatic disorders	5 (12)	5 (12)	9 (22)	9 (22)
Cardiac disorders	2 (5)	2 (5)	5 (12)	5 (12)
General disorders	14 (34)	14 (34)	14 (34)	14 (34)
Metabolism disorders	10 (24)	10 (24)	10 (24)	10 (24)
Nervous system disorders	2 (5)	2 (5)	0	0
Renal disorders	0	0	1 (2)	1 (2)
Respiratory disorders	7 (17)	7 (17)	5 (12)	5 (12)
Skin & subcutaneous disorders	2 (5)	2 (5)	4 (10)	4 (10)
Vascular disorders	4 (10)	4 (10)	3 (7)	3 (7)

65-75 y/o subjects

Similar frequency across groups except for higher incidence in the HES 450 treatment arm for "any AE", blood & lymphatic disorders, general disorders, renal disorders, skin & subcutaneous disorders, and vascular disorders. See table 14.

Table 14: AEs in Subjects 65-75 y (Source: Sponsor)				
	6% HES 130/0.4 N=118 (%)	HES 130 Total N=161 (%)	HES 450 N=11	All Controls N=137
Any AE	69 (59)	96 (60)	11 (100)	81 (59)
Blood & lymphatic disorders	12 (10)	13 (8)	6 (55)	8 (6)
Cardiac disorders	25 (21)	31 (19)	2 (18)	26 (19)
General disorders	12 (10)	14 (9)	7 (64)	14 (10)
GI disorders	26 (22)	33 (21)	6 (55)	26 (19)
Metabolism disorders	10 (9)	14 (9)	0	16 (12)
Nervous system disorders	10 (9)	20 (12)	0	9 (7)
Renal disorders	5 (4)	5 (3)	3 (27)	11 (8)
Respiratory disorders	9 (8)	14 (9)	0	7 (5)
Skin & subcutaneous disorders	9 (8)	17 (11)	2 (18)	5 (4)
Vascular disorders	15 (13)	24 (15)	4 (36)	22 (16)

>75 y/o subjects

Similar frequency across groups except for a higher incidence in the HES 450 treatment arm for "any AE", blood & lymphatic disorders, GI disorders, nervous system disorders, renal disorders, and respiratory disorders. See table 15.

Table 15: AEs in Subjects >75 y (Source: Sponsor)				
	6% HES 130/0.4 N=31 (%)	HES 130 Total N=45 (%)	HES 450 N=8	All Controls N=43
Any AE	25 (81)	38 (85)	8 (100)	31 (72)
Blood & lymphatic disorders	7 (23)	8 (18)	4 (50)	6 (14)
Cardiac disorders	4 (13)	11 (24)	2 (25)	13 (30)
General disorders	10 (32)	17 (38)	3 (38)	6 (14)
GI disorders	12 (39)	17 (38)	5 (63)	14 (33)
Metabolism disorders	8 (26)	13 (29)	2 (25)	10 (23)
Nervous system disorders	4 (13)	9 (20)	2 (25)	5 (12)
Renal disorders	2 (7)	3 (7)	3 (38)	4 (9)
Respiratory disorders	6 (20)	9 (20)	4 (50)	7 (16)
Skin & subcutaneous disorders	6 (20)	7 (16)	2 (25)	3 (7)
Vascular disorders	7 (23)	8 (18)	2 (25)	8 (19)

3.7 Dose-response

The frequency of "any AE" in the 6% HES 130/0.4 treatment arm was *lower* in the *high* dose range (>4000 mL: 44.8%) than in the low dose range (\leq 1000 mL: 55.2%).

A similar pattern was observed for the HES 130 total group (48.1% vs. 55.7%). For the >1000 - 2000 mL and >2000 - 3000 mL dosing cohorts, respective frequencies were 60.8% and 53.7%.

3.8 Adverse events & related clinical laboratory values

Similar incidence except for excess "any severe AE" in the HES 450 treatment arm. See table 16.

Table 16: Subjects with ≥1 Adverse Events by Treatment Group in Controlled Studies (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Any AE	271 (57.5)	413 (53.8)	51 (100)	312 (57.0)
Any AE leading to death	6 (1.3)	11 (1.4)	0	10 (1.8)
Any AE leading to withdrawal	5 (1.1)	16 (2.1)	2 (3.9)	10 (1.8)
Any nonfatal SAE	38 (8.1)	50 (6.5)	5 (9.8)	43 (7.9)
Any severe AE	42 (8.9)	67 (8.7)	11 (21.6)	58 (10.6)

Cardiac AEs

Similar frequency across treatment groups. See table 17.

Table 17: Cardiac AEs by Treatment Group in Controlled Studies (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Cardiac disorders	64 (13.6)	87 (11.3)	8 (15.7)	75 (13.7)
Atrial fibrillation	7 (1.5)	10 (1.3)	1 (2.0)	21 (3.8)
Myocardial infarction	6 (1.3)	7 (0.9)	0	3 (0.5)
Myocardial ischemia	1 (0.2)	1 (0.1)	0	0
Heart failure	3 (0.6)	5 (0.7)	0	2 (0.4)
Ventricular fibrillation	2 (0.4)	2 (0.3)	0	1 (0.2)
Cardiac arrest	1 (0.2)	1 (0.1)	0	2 (0.4)

Vascular and bleeding AEs

Reported *more frequently* for “any hemorrhage” and “coagulopathy” in the HES 450 cohort. See table 18.

Table 18: Vascular and Bleeding Disorders by Treatment Group — Controlled Studies (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Vascular disorders	51 (10.8)	70 (9.1)	15 (29.4)	58 (10.6)
Any hemorrhage	37 (7.9)	39 (5.1)	7 (13.7)	42 (7.7)
Post procedural hemorrhage	10 (2.1)	10 (1.3)	0	11 (2.0)
Hemorrhage NOS	5 (1.1)	5 (0.7)	0	11 (2.0)
Cerebral hemorrhage	2 (0.4)	3 (0.4)	0	6 (1.1)
Coagulopathy	3 (0.6)	3 (0.4)	3 (5.9)	4 (0.7)
Epistaxis	2 (0.4)	2 (0.3)	1 (2.0)	2 (0.4)
Extradural hemotoma	2 (0.4)	2 (0.3)	0	0
Hematemesis	2 (0.4)	2 (0.3)	1 (2.0)	1 (0.2)
Hematoma NOS	2 (0.4)	2 (0.3)	1 (2.0)	1 (0.2)
Intracranial hemorrhage NOS	2 (0.4)	2 (0.3)	0	0
Wound hemorrhage	1 (0.2)	1 (0.1)	0	0

Changes in hemostasis

When compared against HES 200, **estimated blood loss (EBL)** was lower (mean 2115 mL vs. 3087 mL) and **factor VIII activity** and **vWF antigen** were both *higher* in 6% HES 130/0.4 subjects (see tables 19 and 20).

When compared against 450/0.7, subjects treated with 6% HES 130/0.4 experienced (a) a trend towards reduced EBL, (b) a reduced need of RBC transfusions (8.0 vs. 13.8 mL/kg) (exploratory analysis), and (c) less influence on coagulation parameters at several time points, as follows:

- **Platelets: decreased equally** in HES 130 Total and Control Total. Data missing for HES 450 cohort.
- **PTT: no difference** across groups

- *vWF (Ristocetin cofactor)*: rebounded earlier and to a higher degree in test arm subjects compared to controls, e.g., levels were significantly higher at 24 and 48 h (HS-13-30-US), 4-6 h post-surgery (HS-13-13-DE), and on the 1st postoperative day (HS-13-19-FR).
- *Factor VIII*: rebounded earlier and to a higher degree in test arm subjects compared to controls, e.g., levels were significantly higher at 24 and 48 h (HS-13-30-US), and 4-6 h post surgery (HS-13-13-DE, HS-13-14-NL).

See tables 19-22a

Table 19: FVIII in Studies Where Captured (Source: FDA analysis of line listings)		
Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HS-13-13-DE: 6% HES 130 vs. 6% HES 200 (N=26 vs. 26)		
Baseline (N=24 vs. 25)	43	46
End of surgery (N=19 vs. 18)	26 (60)	26 (57)
4-6 h (N=23 vs. 24)	36 (84)	35 (76)
1 day after surgery (N=4 vs. 1)	57 (133)	46 (100)
HS-13-19-FR: 6% HES 130 vs. 6% HES 200 (N= 52 vs. 48)		
Baseline (N=49 vs. 44)	115	127
End of surgery (N=48 vs. 43)	95 (83)	98 (77)
4-6 h (N=48 vs. 45)	148 (129)*	139 (109)
HS-13-24-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=31 vs. 30)		
Baseline (N=30 vs. 29)	136	133
After 45 mL/kg of solution (N=30 vs. 28)	109 (80)	116 (87)
24 h (N=30 vs. 28)	130 (96)	134 (100)
48 h (N=30 vs. 28)	164 (121)	169 (127)
HS-13-25-CH: 6% HES 130/0.4 vs. 6% HES 200 (N= 16 vs. 15)		
Baseline (N=16 vs. 16)	83	89
Day 2 (N=16 vs. 14)	81 (98)	85 (96)
Day 4 (N=13 vs. 15)	135 (163)*	107 (120)
Day 6 (N=9 vs. 14)	153 (184)	142 (160)
Day 8 (N=6 vs. 12)	141 (170)	144 (162)
3 days after last infusion (N=13 vs. 10)	170 (205)	156 (175)
HS-13-30-US: 6% HES 130/0.4 vs. HES 450 (N=49 vs. 51)		
Baseline (N=49 vs. 50)	146	143
2 h post-surgery (N=49 vs. 48)	158 (108)	130 (91)
24 h (N=49 vs. 46)	239 (164)***	146 (102)
48 h (N=49 vs. 44)	315 (216)***	228 (159)

p-value of t-test comparing test versus control based on change from baseline. *p<0.05; ***p<0.001. As noted earlier, FVIII results for HS-13-30-US were considered *exploratory*.

Table 20: vWF in Studies Where Captured (Source: FDA analysis of line listings)		
Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HS-13-13-DE: 6% HES 130 vs. 6% HES 200 (N=26 vs. 26)		
Baseline (N=25 vs. 25)	60	56
End of surgery (N=19 vs. 17)	47 (78)	32 (57)
4-6 h (N=23 vs. 23)	60 (100)	38 (68)
24 h (N=4 vs. 1)	61 (100)	76 (136)
HS-13-19-FR: 6% HES 130 vs. 6% HES 200 (N= 52 vs. 48)		
Baseline (N=51 vs. 44)	107	112
End of surgery (N=49 vs. 43)	83 (78)	84 (75)
4-6 h (N=49 vs. 46)	144 (135)	132 (118)
HS-13-24-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=31 vs. 30)		
Baseline (N=30 vs. 29)	133	134
After 45 mL/kg of solution (N=31 vs. 29)	137 (103)	157 (117)
24 h (N=31 vs. 29)	188 (141)	175 (131)
48 h (N=31 vs. 28)	219 (165)	211 (158)
HS-13-30-US: 6% HES 130/0.4 vs. HES 450 (N=49 vs. 51)		
Baseline (N=49 vs. 50)	133	135
2 h post-surgery (N=49 vs. 48)	135 (102)*	113 (84)
24 h (N=49 vs. 46)	220 (165)***	147 (109)
48 h (N=49 vs. 44)	259 (195)***	211 (156)

p-value of t-test comparing test versus control based on change from baseline. *p<0.05; ***p<0.001. As noted earlier, vWF results for HS-13-30-US were considered *exploratory*.

Table 21: Platelet counts in Studies Where Captured (FDA analysis of line listings)		
Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HE-13-13-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=26 vs. 26)		
Baseline (N=24 vs. 26)	229	240
End of surgery (N=20 vs. 22)	180 (79)	169 (70)
4-6 h after end of surgery (N=26 vs. 24)	154 (67)	157 (65)
24 h after end of surgery (N=25 vs. 26)	179 (78)	165 (69)
HS-13-14-NL: 6% HES 130/0.4 vs. 6% HES 200 (N=30 vs. 32)		
Baseline (N=28 vs. 29)	192	181
After ECC (after protamine administration) (N=28 vs. 28)	115 (60)	114 (63)
Arrival in the ICU (N=27 vs. 30)	135 (70)	121 (67)
1 st post-operative morning (N=28 vs. 30)	174 (91)	153 (85)
HS-13-18-BE: 6% HES 130/0.4 vs. 6% HES 200 (N=20 vs. 20)		
Baseline (N=20 vs. 20)	248	219
Admission to PACU (N=20 vs. 20)	175 (71)	155 (71)
1 st post-operative morning (N=20 vs. 20)	156 (63)	138 (63)
HS-13-19-FR: 6% HES 130 vs. 6% HES 200 (N= 52 vs. 48)		
Baseline (N=51 vs. 47)	239	243
End of surgery (N=48 vs. 47)	179 (75)	173 (71)
4-6 h after end of surgery (N=52 vs. 47)	185 (77)	169 (70)
24 h (N=51 vs. 46)	195 (82)	186 (77)
HS-13-21-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=10 vs. 10)		
Baseline (N=10 vs. 10)	244	242
30 min after end of infusion (N=10 vs. 10)	187 (77)	178 (74)
1 st post-operative day (N=10 vs. 10)	169 (69)	176 (73)
HS-13-24-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=31 vs. 30)		
Baseline (N=30 vs. 30)	213	202
After 45 mL/kg of solution (N=31 vs. 29)	135 (63)	134 (66)
24 h after start of infusion (N=31 vs. 30)	162 (76)	143 (71)

48 h after start of infusion (N=31 vs. 29)	150 (70)	141 (70)
HS-13-25-CH: 6% HES 130/0.4 vs. 6% HES 200 (N=16 vs. 15)		
Baseline (N=16 vs. 15)	155	179
Day 2 (N=16 vs. 15)	123 (79)	132 (74)
Day 4 (N=13 vs. 15)	137 (88)	135 (75)
Day 6 (N=9 vs. 14)	153 (99)	176 (98)
3 days after last infusion (N=12 vs. 12)	326 (210)	441 (246)
HS-13-27-DE: 6% HES 130/0.4 vs. 5% albumin (N=41 vs. 42)		
Baseline (N=20 vs. 23)	366	397
1 st post-operative day (N=37 vs. 40)	313 (86)	336 (85)
HS-13-30-US: 6% HES 130/0.4 vs. HES 450 (N=49 vs. 51)		
Baseline (N=45 vs. 47)	210	203
End of surgery (N=49 vs. 50)	178 (85)	163 (80)
48 h after end of surgery (N=43 vs. 46)	171 (81)	159 (78)
HS-13-35-PL: 6% HES 130/0.4 vs. Gelatin (N=16 vs. 17)		
Baseline (N=16 vs. 17)	184	162
ICU arrival (N=16 vs. 17)	150 (82)	135 (83)
1 st post-operative morning (N=16 vs. 17)	152 (83)	137 (85)

Table 22: Ristocetin Values Where Captured (Source: FDA analysis of line listings)		
Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HS-13-13-DE: 6% HES 130 vs. 6% HES 200 (N=26 vs. 26)		
Baseline (N=24 vs. 26)	98	110
End of surgery (N=19 vs. 18)	79 (81)	70 (64)
4-6 h after end of surgery (N=23 vs. 23)	102 (104)	79 (72)
HS-13-14-NL: 6% HES 130/0.4 vs. 6% HES 200 (N=30 vs. 32)		
Baseline (N=28 vs. 29)	151	166
After ECC (after protamine infusion) (N=28 vs. 30)	129 (85)	142 (86)
1 st post-operative morning (N=27 vs. 29)	223 (148)	184 (111)
HS-13-19-FR: 6% HES 130 vs. 6% HES 200 (N= 52 vs. 48)		
Baseline (=49 vs.47)	94	116
End of surgery (N=50 vs. 43)	87 (93)	81 (70)
4-6 h after end of surgery (N=48 vs. 46)	142 (151)	134 (116)
HS-13-24-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=31 vs. 30)		
Baseline (N=30 vs.29)	158	152
After 45 mL/kg of solution (N=30 vs.28)	237 (150)	220 (145)
24 h (N=30 vs.28)	259 (164)	234 (154)
48 h (N=30 vs. 28)	328 (208)	311 (205)
HS-13-25-CH: 6% HES 130/0.4 vs. 6% HES 200 (N=16 vs. 15)		
Baseline (N=16 vs.15)	107	120
Day 2 (N=16 vs. 14)	143 (134)	114 (95)
Day 4 (N=13 vs. 15)	164 (153)	141 (118)
Day 6 (N=9 vs. 14)	167 (156)	139 (116)
3 days after last infusion (N=13 vs. 10)	172 (161)	169 (141)

Table 13. Summary of Factor VIII and Ristocetin in Phase 3 Trials (Source: sponsor) (Blue: p<0.05)			
Study	Parameter	Time Point	6% HES 130 — 6% HES 200 Estimate (95% Confidence Interval)
<u>HS-13-13-DE</u>			
	Factor VIII antigen	End of surgery	-0.70 (-19.39, 17.99)
		4-6 h after end of surgery	19.65 (1.05, 38.25)
		1 day after end of surgery	Missing data
	Factor VIII	End of surgery	2.34 (-7.50, 12.19)
		4-6 h after end of surgery	19.65 (1.05, 38.25)
		1 day after end of surgery	Missing data
	vWF (Ristocetin cofactor)	End of surgery	19.83 (-12.19, 51.86)
		4-6 h after end of surgery	33.70 (5.91, 61.48)
		1 day after end of surgery	Missing data
<u>HS-13-14-NL</u>			
	vWF (Ristocetin cofactor)	After weaning from CPB	1.6 (-16.4, 19.6)
		ICU arrival	8.4 (-9.9, 26.6)
		1 st postoperative morning	57.2 (30.2, 84.1)
<u>HS-13-19-FR</u>			
	Factor VIII	Switch from HES to other	-42.9 (-90.5, 4.7)
		End of surgery	5.4 (-17.4, 28.2)
		4-6 h after end of surgery	40.3 (2.9, 77.8)
	Factor VIII antigen	Switch from HES to other	-18.1 (-59.3, 23.2)

vWF (Ristocetin cofactor)	End of surgery	10.8 (-6.5, 28.2)
	4-6 h after end of surgery	16.0 (-6.8, 38.8)
	Switch from HES to other	53.5 (-3.2, 110.2)
	End of surgery	13.8 (-4.2, 31.7)
	4-6 h after end of surgery	17.3 (-6.3, 40.9)

a = difference in means

Estimated blood loss: *similar* across treatment groups. See table 23.

Table 23: Estimated Blood Loss in Volume Replacement Studies (Source: Sponsor)			
	HES 130 Total* N=768	HES 450 N=51	Control Total N=547
Mean ± SD	2115± 1888	1923± 2110	2413± 2437
Minimum	0	100	0
25%	500	800	500
Median	1485	1305	1875
75%	3416	2000	3765
Maximum	12581	10789	21380
N (% of Subjects)	320 (42%)	51 (100%)	319 (58%)

*6% HES 130/0.4 comprised 61% of HES 130 Total subjects

Transfusion of blood products: *similar* volumes of RBC, FFP, and platelets were administered across treatment groups, although the number of subjects who required such products was *noticeably higher* in the HES 450 treatment arm. See table 24.

Table 24: Transfusion of Blood Components in Volume Replacement Studies (Source: Sponsor)			
	HES 130 Total* N=320	HES 450 N=51	Control Total N=319
RBC (Mean ± SD)	956 ± 954	1041 ± 759	924 ± 1544
N (% of Subjects)	89 (28)	28 (55)	116 (36)
FFP (Mean ± SD)	1459 ± 1920	1830 ± 767	1544 ± 2330
N (% of Subjects)	59 (18)	4 (78)	52 (16)
Platelets (Mean ± SD)	431 ± 348	452 ± 146	657 ± 635
N (% of Subjects)	14 (4)	4 (8)	16 (5)

*6% HES 130/0.4 comprised 61% of HES 130 Total subjects

3.9 Clinical laboratory investigations

Serum Ca⁺² and K⁺: No differences. See table 25.

Serum Ionized Calcium and Potassium Values in Controlled Studies (Source: Sponsor)				
Study Time	HES 130 Total* Mean ± SD	HES 200 Mean ± SD	HES 450 Mean ± SD	All Controls Mean ± SD
Calcium				
Baseline	2.31 ± 0.19	2.29 ± 0.15	MD	2.31 ± 0.15
End of Surgery	1.80 ± 0.21	1.80 ± 0.19	MD	1.80 ± 0.19
4-8 h post-surgery	1.93 ± 0.26	1.81 ± 0.17	MD	1.84 ± 0.19
24 h post 1 st dose	2.06 ± 0.25	1.97 ± 0.14	MD	2.08 ± 0.55
Potassium				
Baseline	4.05 ± 0.50	3.97 ± 0.53	3.94 ± 0.50	4.01 ± 0.53
End of Surgery	4.05 ± 0.48	3.97 ± 0.36	4.09 ± 0.56	4.03 ± 0.46
4-8 h post-surgery	3.99 ± 0.54	3.95 ± 0.61	MD	3.96 ± 0.60
24 h post 1 st dose	4.20 ± 0.50	4.32 ± 0.61	MD	4.25 ± 0.59

*6% HES 130/0.4 comprised 61% of HES 130 Total subjects

α-amylase: absolute values (mean) and number of subjects with abnormally elevated levels of α-amylase were *lower* in the 6% HES 130/0.4 arm (54.0 U/L and 2 or 4.9%, respectively) at 48 h postoperative, compared to HES 450 subjects (95.5 U/L and 14 or 35.9% of subjects). Similar trends were evident at 24 h (44.1% vs. 73.6%).

See also table 26 showing lower values when compared to HES 200

Table 26: Amylase in Volume Replacement Studies (FDA analysis of line listings)		
Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HE-13-13-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=26 vs. 26)		
Baseline (N=22 vs. 23)	57	61
24 h after end of surgery (N=24 vs. 25)	118 (207)	189 (310)
HS-13-14-NL: 6% HES 130/0.4 vs. 6% HES 200 (N=30 vs. 32)		
Baseline (N=29 vs. 32)	72	89
1 st post-operative morning (N=28 vs. 28)	319 (443)	559 (628)
2 nd post-operative morning (N=8 vs. 12)	202 (281)	438 (492)
HS-13-18-BE: 6% HES 130/0.4 vs. 6% HES 200 (N=20 vs. 20)		
Baseline (N=14 vs. 15)	129	144
Admission to PACU (N=19 vs. 19)	145 (112)	145 (100)
1 st post-operative morning (N=18 vs. 18)	284 (220)	366 (254)
HS-13-19-FR: 6% HES 130 vs. 6% HES 200 (N= 52 vs. 48)		
Baseline (N=46 vs. 42)	74	73
24 h post-surgery (N=49 vs. 46)	156 (211)	255 (349)
HS-13-24-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=31 vs. 30)		
Baseline (N=31 vs. 30)	55	64
24 h after start of infusion (N=31 vs. 29)	280 (509)	356 (556)
48 h after start of infusion (N=31 vs. 30)	116 (211)	278 (434)
HS-13-25-CH: 6% HES 130/0.4 vs. 6% HES 200 (N=16 vs. 15)		
Baseline (N=15 vs. 15)	33	31
Day 4 (N=12 vs. 10)	128 (388)	101 (326)
Day 8 (N=6 vs. 11)	91 (276)	179 (577)
HS-13-27-DE: 6% HES 130/0.4 vs. 5% albumin (N=41 vs. 42)		
Baseline (N=18 vs. 28)	35	29
1 st post-operative day (N=33 vs. 34)	49 (140)	21 (72)
HS-13-30-US: 6% HES 130/0.4 vs. HES 450 (N=49 vs. 51)		
Baseline (N=49 vs. 47)	64	56

End of surgery (N=49 vs. 48).	68 (106)	61 (109)
48 h after end of surgery (N=42 vs.42)	65 (102)	125 (223)
HS-13-35-PL: 6% HES 130/0.4 vs. Gelatin (N=16 vs.17)		
Baseline (N=16 vs.15)	55	57
1 st post-operative morning (N=15 vs.15)	129 (235)	119 (209)
2 ⁿ post-operative morning (N=13 vs.12)	83 (151)	104 (182)
HS-13-36-FR: 6% HES 130/0.4 vs. Gelatin (N=32 vs. 33)		
Baseline (N=26 vs. 29)	60	65
Day 2 (N=28 vs.26)	189 (315)	181 (279)
Day 3 (N=27 vs.28)	115 (192)	104 (183)
Day 6 (N=24 vs.27)	59 (98)	55 (85)
Day of Discharge (N=20 vs.18)	57 (95)	74 (114)

LFTs: study protocols excluded subjects with “oliguria or anuria not related by hypovolemia”. Mean values were *similar* between 6% HES 130/0.4 and HES 450. See table 27.

Table 27: Final LFT Values – Controlled Studies (Source: Sponsor)			
	HES 130 Total [N=768] (%)*	HES 450 [N=51] (%)	Control Total [N=547] (%)
	Mean ± SD	Mean ± SD	Mean ± SD
ALT	27.5 ± 51.8	24.6 ± 12.1	27.6 ± 49.7
AST	29.5 ± 84.3	33 ± 24.8	31.5 ± 108.5
GGTP	24.6 ± 35.2	25.4 ± 21.8	27.3 ± 44.0
AP	110.9 ± 64.5	MD	111.8 ± 50.0
T Bili	11.0 ± 6.5	9.7 ± 4.9	11.1 ± 10.1

*6% HES 130/0.4 comprised 61% of HES 130 Total subjects

Renal function: **88.9% of subjects (N=1169) had normal SCr values at baseline.** No specific risk for worsening of SCr was observed for subjects >75 y/o, including the subgroup with SCr above ULN at baseline. No difference was found between the HES total group and control total for the proportion of subjects with a ≥2 X increase in SCr: 9 (1.2%) vs. 7 (1.3%).

Cl_{Cr} was specifically measured only in studies HS-13-36-FR (N=65) and HS-13-28-DE (N=19). The latter was designed to specifically evaluate pK and renal function in subjects with **mild to severe** renal impairment after administration of 6% HES 130/0.4. This study also included measurement of Cl_{Cr} at 24-48 h and 48-72 h post infusion. Overall, no relevant deterioration of creatinine clearance was observed during the course of the study.

Study HS-13-36-FR investigated the effects of 6% HES 130/0.4 on postoperative renal function in subjects undergoing aortic surgery. The control group received gelatin solution. The study population comprised subjects >18 y/o with preoperative creatinine clearance ≤80 mL/min. The primary endpoint was peak increase in SCr until Day 6 or discharge, if earlier. Secondary parameters were the incidence of postoperative renal dysfunction, minimum postoperative creatinine clearance, incidence of oliguria, and urinary NAG.

No statistically significant differences between treatment groups were seen.

In study **HS-13-25-CH**, high doses of 6% HES 130/0.4 up to 70 mL/kg were administered over several days in TBI subjects. Cl_{Cr} and mean SCr remained WNL during the entire study in both groups.

See table 28 and 29 and section following (Renal and urinary disorders). Also, see page 59 for discussion of putative effects on renal function.

Table 2. SCr (umol/L) by Cohort, Age, and Baseline SCr — Controlled Studies (Source: Sponsor)				
	HES 130 Total [N=768]*	HES 450 [N=51]	Control Total [N=547]	
	Mean ± SD	Mean ± SD	Mean ± SD	
Adults				
Baseline	81.3 ± 27.5	79.1 ± 21.8	78.5 ± 24.6	
Final value	83.3 ± 31.1	81.7 ± 30.7	82.7 ± 41.2	
Age ≤2 y cohort				
Baseline	30.8 ± 12.7	MD	27.3 ± 8.5	
24 h post 1 st dose	30.4 ± 14.3	MD	26.7 ± 11.8	
Age 3-17 y cohort				
Baseline	MD	MD	123.8	
24 h post 1 st dose	MD	MD	MD	
Age 18-64 y cohort				
Baseline	81.3 ± 24.6	75.3 ± 23.2	79.5 ± 18.0	
24 h post 1 st dose	84.1 ± 29.5	74.3 ± 23.2	80.0 ± 16.2	
Age 65-75 y cohort				
Baseline	88.4 ± 23.8	85.1 ± 15.5	86.2 ± 23.1	
24 h post 1 st dose	90.6 ± 27.7	MD	92.7 ± 36.3	
Age >75 y cohort				
Baseline	98.9 ± 32.2	87.1 ± 21.9	93.8 ± 23.6	
24 h post 1 st dose	102.5 ± 37.7	82.8 ± 23.8	101.6 ± 35.3	
SCr >ULN at baseline cohort				
Baseline	127.9 ± 47.3	145.9 ± 31.3	114.3 ± 21.6	
24 h post 1 st dose	126.6 ± 52.1	132.6 ± 25.0	107.5 ± 32.9	

*6% HES 130/0.4 comprised 61% of HES 130 Total subjects

**HES 450 was the control in the only US (orthopedic surgery) trial

Table 29: Calculated Creatinine Clearance in Study HS-13-25-CH (Source: Sponsor)				
Creatinine Clearance (mL/min)	6% HES 130/0.4 (N=16)		HES 200 N=15)	
	N	Median	N	Median
Day 2	14	111	14	115
Day 4	13	108	13	119
Day 8	4	97	10	109
Day 12	1	48*	8	106
3 day follow up	10	113	9	131

*Sponsor indicates probable urine collection error on Day 12. Three-day follow-up: calculated creatinine clearance 113 mL/min for this subject. Serum creatinine level unchanged from Day 12 to 3-day follow-up (0.8 umol/mL), baseline 0.8 umol/mL.

3.10 Renal and urinary disorders

Similar frequency across groups except for increased incidence in the HES 450 treatment arm. See table 30. See page 59 for discussion of putative effects on renal function.

Table 30: Renal disorders: All Subjects and SCr>ULN Subgroup — Controlled Studies (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
All subjects				
Renal and urinary disorders	14 (3.0)	18 (2.3)	11 (21.6)	30 (5.5)
Oliguria/anuria	4 (0.8)	6 (0.8)	0	10 (1.8)
Renal failure NOS	2 (0.4)	3 (0.4)	0	2 (0.4)
Subgroup: SCr >ULN at baseline				
	N=45	N=71	N=2	N=56
Renal and urinary disorders	1 (2.2)	3 (4.2)	2 (100)	6 (10.7)
Oliguria/anuria	0	1 (1.4)	0	1 (1.8)
Renal impairment NOS	0	0	0	1 (1.8)
Acute renal failure NOS	0	0	1 (50.0)	2 (3.6)

3.11 Nervous system disorders

Similar frequency across groups except for increased incidence in the HES 450 treatment arm. See table 31.

Table 31: Nervous System Disorders — Controlled Studies (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Nervous system disorders	53 (11.3)	103 (13.4)	14 (27.5)	63 (11.5)
Cerebral hemorrhage	2 (0.4)	3 (0.4)	0	(6 (1.1)
CVA/TIA	1 (0.2)	4 (0.5)	0	1 (0.2)

3.12 Respiratory, thoracic and mediastinal disorders

Similar frequency across groups except for increased incidence in the HES 450 treatment arm. See table 32.

Table 32: Respiratory System Disorders — Controlled Studies (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Respiratory system disorders	45 (9.6)	56 (7.3)	13 (25.5)	39 (7.1)
Respiratory failure	5 (1.1)	5 (0.7)	0	0
ARDS	1 (0.2)	1 (0.1)	0	1 (0.2)

3.13 Skin and subcutaneous tissue disorders

Similar frequency across groups except for increased pruritus (19.6%) in the HES 450 treatment arm. See table 33.

Table 33: Skin & Subcutaneous Tissue Disorders — Controlled Studies (Source: Sponsor)				
	6% HES 130/0.4 N=471 (%)	HES 130 Total N=768 (%)	HES 450 N=51 (%)	Control Total N=547 (%)
Skin and subcutaneous tissue	37 (7.9)	71 (9.2)	10 (19.6)	39 (7.1)
Pruritus	23 (4.9)	49 (6.4)	5 (9.8)	24 (4.4)

3.14 AEs in special populations

Elderly subjects: in subjects 65-75 years old, no differences were noted in the frequency of any reported AE except for **nervous system disorders**, which were 12.4% vs. 6.6% (normal saline) in the stroke studies. In subjects >75 years old, HES 130/0.4 appeared as safe as HES 450.

Non-dialysis-dependent renally impaired subjects: In terms of safety, no serious or life-threatening AEs were reported and no subject had to terminate the study prematurely due to an AE. Events of mild severity included visual disturbances, eye pain, UTI and headache; events of moderate severity included nausea, migraine, and increase in blood pressure. All events resolved within 1 day except for a UTI, whose etiology and outcome are unknown.

Hypertensive subjects: one quarter of the Overall Safety Analysis population comprised subjects with baseline or PMH of hypertension (mostly Caucasian).

3.15 Death narratives

HS-13-24: control group (HES 200)

1. Subject # 31 was suddenly pulseless at the end of CABG while being lifted from the OR table into her bed. Emergency thoracotomy showed an insufficient aortic suture with surgical bleeding leading to tamponade as the event. After aortic suture and surgical hemostasis, bleeding continued in the ICU despite administration of coagulation factors. The subject died 3 days later. At autopsy, there was aortic dissection evident, which was the cause of death.

HS-13-25-CH: test group (6% HES 130/0.4)

1. Subject #14, a 22 y/o male experienced severe TBI. He was administered a total of 4000 mL of study solution, 1500 mL of which was infused prior to initiation of barbiturate coma for intractable intracranial hypertension. The following day, transcranial doppler showed absent cerebral blood flow. According to the sponsor, the primary bleeding resulting from the accident was most likely responsible for elevation in ICP. No sign of a coagulation disturbance was present and therefore, a relationship to study drug was considered unlikely.
2. Subject #16, a 35 y/o male also experienced severe TBI. On the second treatment day, the subject developed a massive secondary hemorrhage into the left hemisphere. Because of the nature of the primary injury and the fact that at the time of secondary bleeding no coagulation disturbances were present, relationship to study drug was considered unlikely.
3. Subject #25, a 42 y/o male, presented with TBI, including midline shift and fixed left pupil. The next day, bilateral bleeding into the ventricles was diagnosed. The subject had received 2000 mL of study solution prior to this event and received another 2500 after it. Except for thrombocytopenia, there were no signs of impaired coagulation. The subject was treated with ventricular drainage, but died 10 days later. The SAE "intracranial bleeding" was considered possibly related to study solution by the investigator because it could not be excluded that the resulting hemodilution contributed to the bleeding, despite absent signs of specific coagulation disturbances. Relationship of

study fluid to death was unlikely due to the nature of the primary injuries.

4. Subject #29, a 25 y/o male with severe TBI and subarachnoid hemorrhage underwent barbiturate coma and craniotomy, but died 10 days later. Relationship of the SAE to study solution was considered unlikely.

Control group (HES 200 + albumin group)

1. Subject #3, a 55 y/o male with TBI developed septic shock on the first treatment day. MOF followed and he died of Gram negative septic shock on the second day. Relationship of the SAE to control solution was considered unlikely.
2. Subject #8, a 22 y/o male with TBI experienced subdural hematoma, cerebral edema, and elevated ICP necessitating barbiturate coma. After one week, sepsis with MOF developed and he died the next day. Relationship of the SAE to control solution was considered unlikely.
3. Subject #30, a 42 y/o male with TBI and intracranial bleeding, experienced worsening cerebral edema, followed by anisocoria and paraplegia. He died 8 days later. Relationship of the SAE to control solution was considered unlikely.

HS-13-27-DE: control group (albumin)

1. Subject #23, a 2-month old girl died of cardiac arrest of unclear etiology one day after surgery for cranial synostosis. According to the investigator, the procedure was totally uneventful as was the early postoperative course. EBL was 100 mL and intraoperatively she received 100 mL of 5% albumin in 3 bolus injections via central line. Also, 125 mL of RBC and 570 mL crystalloids were administered intraoperatively. Around midnight, the child stopped breathing and H decreased from 100 to 50 bpm. ECG "did not show sinus rhythm anymore" and CPR was begun, but she soon died. Relationship of the SAE to control solution was considered as "not yet assessable" by the investigator and no follow-up information is available, according to the sponsor.

HS-13-17-DE: test group (10% HES 130/0.4)

1. Subject #49, a 69 y/o male, experienced severe cerebral thrombosis during the second day of HES 130 therapy for a CVA. He died later that day.
2. Subject #59, a 77 y/o female, experienced a CVA 27 days after starting 10% HES 130 therapy. This lead to her demise 3 days later. Relationship to study drug was considered unlikely.
3. Subject #60, an 84 y/o male, suffered severe hypotension 4 days after starting 10% HES 130 therapy. He recovered completely the same day. However, he suffered an MI 65 days after starting the study and died shortly after end of follow-up, about 3 months after end of study medication. Relationship to study drug was negative.
4. Subject #93, a 60 y/o female, experienced a CVA and moderate hypertension during the first day of HES therapy. She died 3 days later. The investigator characterized this as stroke progression and relationship to study drug was considered negative.
5. Subject #115, a 59 y/o female, experienced severe intracranial hypertension and became comatose 2 days after starting HES 130 therapy. She died one day later. Relationship to study ddrug was considered negative.

Control group (normal saline)

1. Subject #24, an 83 y/o female, experienced severe cerebral edema and became comatose 10 days after starting treatment and died that day. Relationship to control solution was considered unlikely.
2. Subject #36, a 78 y/o male, experienced severe sepsis and severe arrhythmias 81 days after starting treatment with saline. He died 7 days later. Relationship to control solution was considered to be negative.
3. Subject #70, a 76 y/o male, experienced severe cardiac failure 9 days after starting treatment with saline. He died 14 days later. Relationship to study solution was considered unlikely.

HS-13-36-FR: test group (6% HES 130/0.4)

1. Subject #411, a 63 y/o male, received 2000 mL of 6% HES 130/0.4 for volume replacement during AAA surgery. Four days later he suffered a cardiac arrest. Resuscitation was unsuccessful and he died. Relationship to test solution was unlikely.
2. Subject #416, a 74 y/o male, received 1000 mL 6% HES 130/0.4 within 1 h intraoperatively. He was discharged and re-hospitalized 3 months later for a colectomy, where he died from a postoperative infarction. Relationship to test solution was unlikely.

Control group (gelatin)

1. Subject #117, a 67 y/o male, received 7000 mL of gelatin for volume replacement during AAA surgery until the second postoperative day. On POD 1, the subject developed acute limb ischemia and was re-operated on. One hour after this second surgery he arrested, but resuscitation was unsuccessful. Relationship to control solution was unlikely.
2. Subject #704, a 65 y/o male, received 2000 mL of gelatin within 9 h on the day of surgery. Postoperatively on the same day, he experienced anuria. The subject required dialysis but died 2.5 months later. Relationship to control solution was negative.

4.0 POST-MARKETING DATA

Over 31.5 millions units of 6% HES 130/0.4 have been sold from European registration in June 1999 until December 2005. Based on the assumption that patients needing volume replacement receive 2000 mL (mean) for an average treatment duration of 1 day, approximately 7.8 million patients have been treated during this time period.

For this time period, 148 SAEs were reported to the sponsor. The majority were reported from clinical trials and one quarter were reported spontaneously or via Health Authorities.

The sponsor classified 73/148 cases as serious (47 cases from clinical trials and 26 reported spontaneously). A total of 32/73 cases were considered probably or possibly related to product administration, or not-assessable. For the remaining 41 cases, the investigator and the sponsor agreed a causal relationship was unlikely, and thus, not reportable.

Since June 1999, there have been 7 reports of subjects who died while participating in clinical trials. In all cases, the sponsor's assessment of causality was "unlikely related". In 2 cases, spontaneous mortality reports were received, both of which were considered to be anaphylactoid reactions and "possibly related" to study drug.

There was no obvious or unexpected accumulation of cases in any particular System Organ Class. Serious cases were most frequently reported under immune system disorders, cardiac disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders.

Two cases of liver disorders from a single clinician were reported as serious and unexpected. The sponsor does not agree that these events were possibly related to the product. Another case was reported from Swiss Medic. Despite pre-existing acute renal insufficiency and start of hemodialysis, 6% HES 130/0.4 was infused, even though administration of the product is contraindicated in patients with acute renal failure.

The sponsor notes an additional clinical trial was performed in China (HS-13-01-CH: "Comparison of 6% HES 130/0.4 HES 130/0.4 and HES 200/0.5 [with pentastarch] in volume replace therapy during noncardiac surgery". In this trial, 109 subjects

received 6% HES 130/0.4 and 106 received pentastarch up to 33 mL/Kg/day. According to the sponsor, there were 108 AEs in the test arm vs. 120 AEs in the pentastarch arm. Most of the AEs were changes/abnormalities in coagulation parameters. Five cases of urticaria or erythema occurred in the test arm, and all were assessed as "possibly related".

The sponsor also notes that it has performed a clinical trial with a product similar to 6% HES 130/0.4 except for the fact that the vehicle is a different from the test product. The product is known as "HES 130/0.4 balanced". In this trial, 20 AEs in this arm have been reported to the sponsor, of which 11 were serious. Two of these have been assessed as "possibly related", while the remaining 9 were considered "unlikely related". For the 2 "possibly related" cases, postoperative bleeding was reported. However, the sponsor does not consider these as unexpected, since subjects were undergoing open heart surgery associated with cardiopulmonary bypass. Two other subjects died in this trial, but in both cases the causal relationship was considered "unlikely", both by the investigator and by the sponsor. Remaining cases have been reported to the SOC "cardiac disorders" (4 cases), injury, poisoning and procedural complications (3 cases), and respiratory disorders (3 cases).

See table 34.

Safety Update Report: Serious and Non-Serious (Source: Sponsor)			
	Serious	Non-Serious	Total # of AEs
Blood & lymphatic disorders	5	0	5
Cardiac disorders	17	1	18
General disorders (pyrexia, MOF, impaired healing)	12	0	12
GI disorders (includes intra-abdominal hemorrhage)	6	1	7
Immune disorders (anaphylaxis, hypersensitivity)	17	0	17
Infectious disorders	15	0	15
Injury, poisoning, & procedure complications (includes hemorrhage during and after surgery)	6	0	6
Investigations	14	0	14
Metabolism disorders (hyperglycemia)	1	0	1
Nervous system disorders (includes ICH)	11	1	12
Renal disorders	11	0	11
Respiratory disorders	20	0	20
Skin & subcutaneous disorders	6	0	6
Vascular disorders (includes hypotension, thrombosis)	15	0	15
Spontaneous/Authority			62
Clinical trial			104
TOTAL	163	3	166

5.0 Literature Review: Putative effect on renal function

The most controversial aspect surrounding use of HES solutions is their putative adverse effect on renal function, especially in patients with pre-existing renal dysfunction. This issue was highlighted by a study published in *Lancet* in 2001 (see abstract, below) comparing a *medium* MW hetastarch (6% HES 200) against 3% gelatin for volume resuscitation of patients with septic shock. Although the authors reported a 2-fold increase in the risk of “acute renal failure” (defined as a doubling of SCr or necessity for dialysis), the actual data show an absolute 3% increase in necessity for dialysis (20 vs. 17%) and increased SCr only on Days 6 and 7 during the 28-day study period.

This study has been criticized because the two cohorts differed at baseline in important respects. For example, more subjects in the HES treatment arm (a) had risk factors for ARF before inclusion (28% vs. 20%), (b) were admitted to the ICU for surgical vs. medical reasons (12% vs. 3%), and (c) received vasoactive drugs during hospitalization (49% vs. 41%).

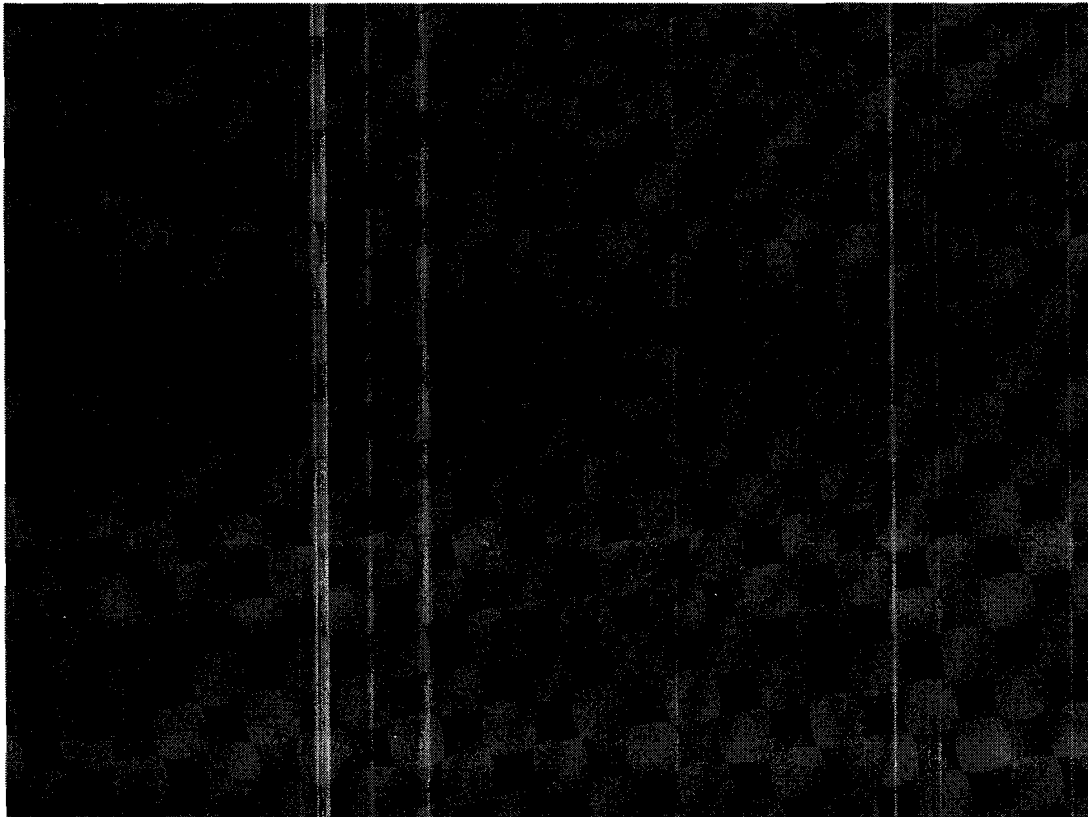
FDA review of the entire NDA AE dataset found 56/1315 subjects who experienced renal system adverse events. Of these 56, 28 had an abnormally elevated SCr at baseline *and* experienced either “acute renal failure (MedDRA terms: renal function abnormal, renal failure NOS, renal failure acute) or oliguria/polyuria (see table 35). For the MedDRA term acute renal failure, there was an imbalance of 4:7 *in favor of* HES 130; the imbalance was in the *same direction* for severe and moderate degrees of severity, as well as for MedDRA terms oliguria and polyuria. Three control subjects but no test subjects experienced a renal SAE.

In summary, there is no evidence in this NDA that 6% HES 130/0.4 adversely impacts renal function in subjects with pre-existing renal dysfunction. What *is* lacking from this NDA is robust evidence in subjects with septic shock that the product is safe. Similar comments pertain to subjects undergoing dialysis.

The following abstracts illustrate the controversy in this domain and lend support for a PMC of Phase 4 RCTs to be conducted by the sponsor in subjects with septic shock and in subjects undergoing hemodialysis who experience hypotension.

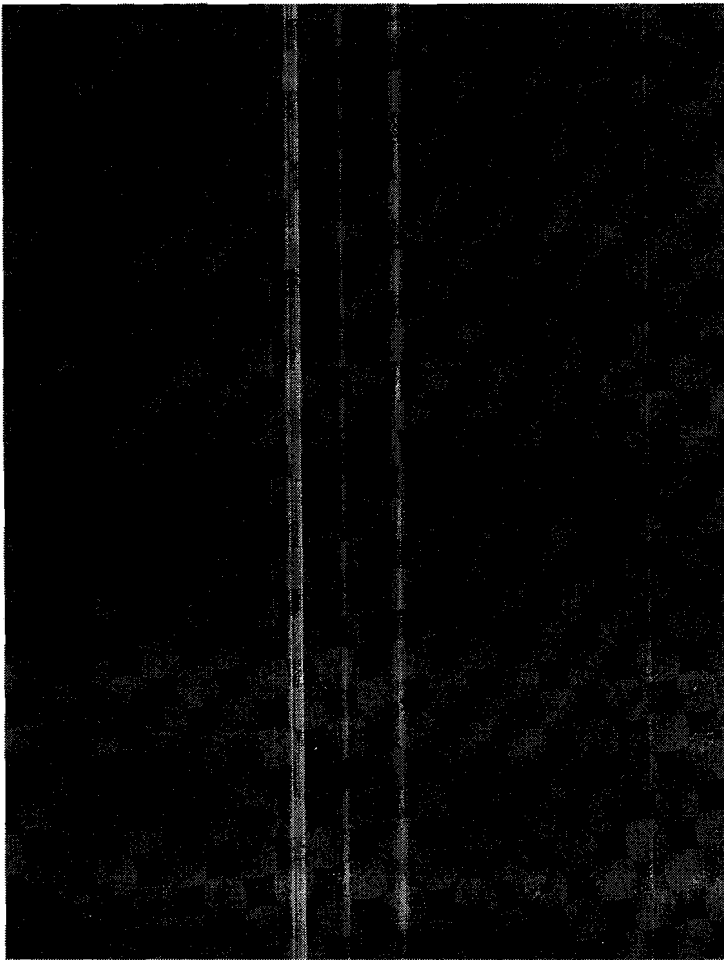
Renal AEs in Subjects at Baseline Who Experienced Renal AEs – Controlled Studies (Source: FDA Clinical Trials Database)			
Study	Arm (# of Subjects)	Event (MedDRA Code)	Severity (# of Subjects)
HS-13-14-NL	Control (1)	Renal function abnormal	Moderate
HS-13-17-DE	10% HES 130 (2)	Renal function abnormal	Mild (1), moderate (1)
	10% HES 130 (2)	Oliguria	Mild (2)
	Control (1)	Oliguria	Moderate (1)
HS-13-19-FR	6% HES 130/0.4 (2)	Oliguria	Mild (2)
HS-13-24-DE	6% HES 130/0.4 (1)	Polyuria	Moderate
	Control (1)	Renal function abnormal	Moderate
HS-13-25-CH	Control (1)	Anuria	Severe
	Control (1)	Renal function abnormal	Severe
HS-13-27-DE	Control (1)	Oliguria	Mild
HS-13-30-US	6% HES 130/0.4 (1)	Renal failure acute	Mild
	Control (1)	Renal failure NOS	Moderate
HS-13-35-PL	6% HES 130/0.4 (1)	Oliguria	Mild
	Control (6)	Oliguria	Mild
HS-13-36-FR	6% HES 130/0.4 (1)	Renal failure NOS	Mild
	Control (3)	Oliguria	Mild
	Control (2)	Renal failure acute	Severe (1), mild (1)

Totals:	10:18	Renal function abnormal, renal failure NOS, renal	Severe=0:3
HES 130:HES 200		failure acute=4:7	Moderate=1:3
			Mild=3:1
		Oliguria=6:10	Moderate=1:1
			Mild=5:10



Br J Anaesth 2007; 98: 216–24

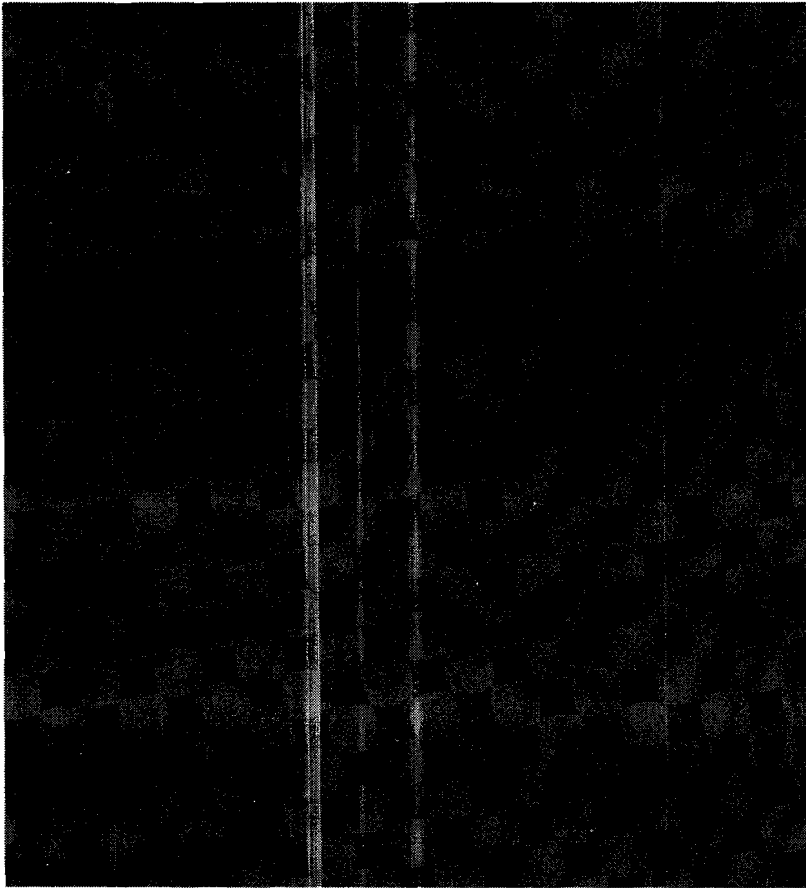
FDA comment: this *post hoc* analysis comes from a multicenter observational study designed to evaluate the epidemiology of sepsis. Using multivariable analysis, the authors report HES was not associated with increased risk for dialysis. This conclusion was challenged in a Letter to the Editor, which cited a number of limitations not mentioned by the authors: the type of HES used was not reported; median stay in the ICU was only 3 days; and the median amount of HES administered was 555 mL per day and median total volume was only 1000 per patient.



Lancet 2001; 357: 911-16

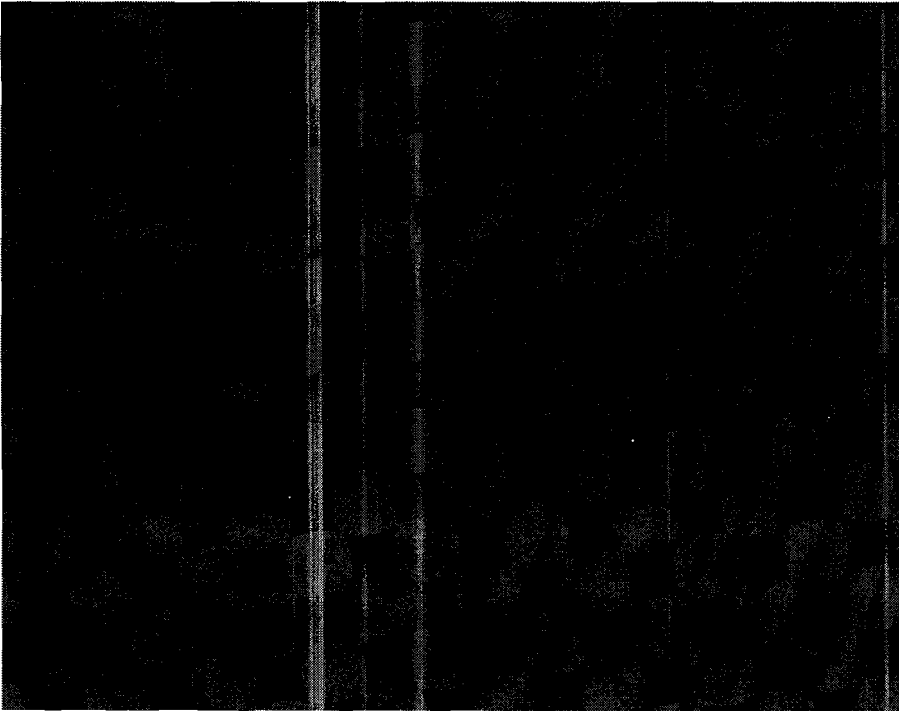
FDA comment: the authors report that use of HES 200/0.5 doubled the risk of "ARF" (1SCr and necessity for dialysis). However, the two cohorts differed at baseline, e.g., more subjects in the HES treatment arm had (a) risk factors for ARF before inclusion (28% vs. 20%), (b) were admitted for surgical vs. medical reasons (12% vs. 3%), and (c) received vasoactive drugs during hospitalization (49% vs. 41%). In addition, baseline mean SCr was higher in HES subjects (143 vs. 114).

Although the authors state "ARF" developed in more HES subjects than gelatin subjects (42% vs. 23%), mean SCr concentrations actually differed *only* on Days 6 and 7 (out of 28 days), and necessity for renal replacement therapy was *no different* overall (20 vs. 17% of subjects).



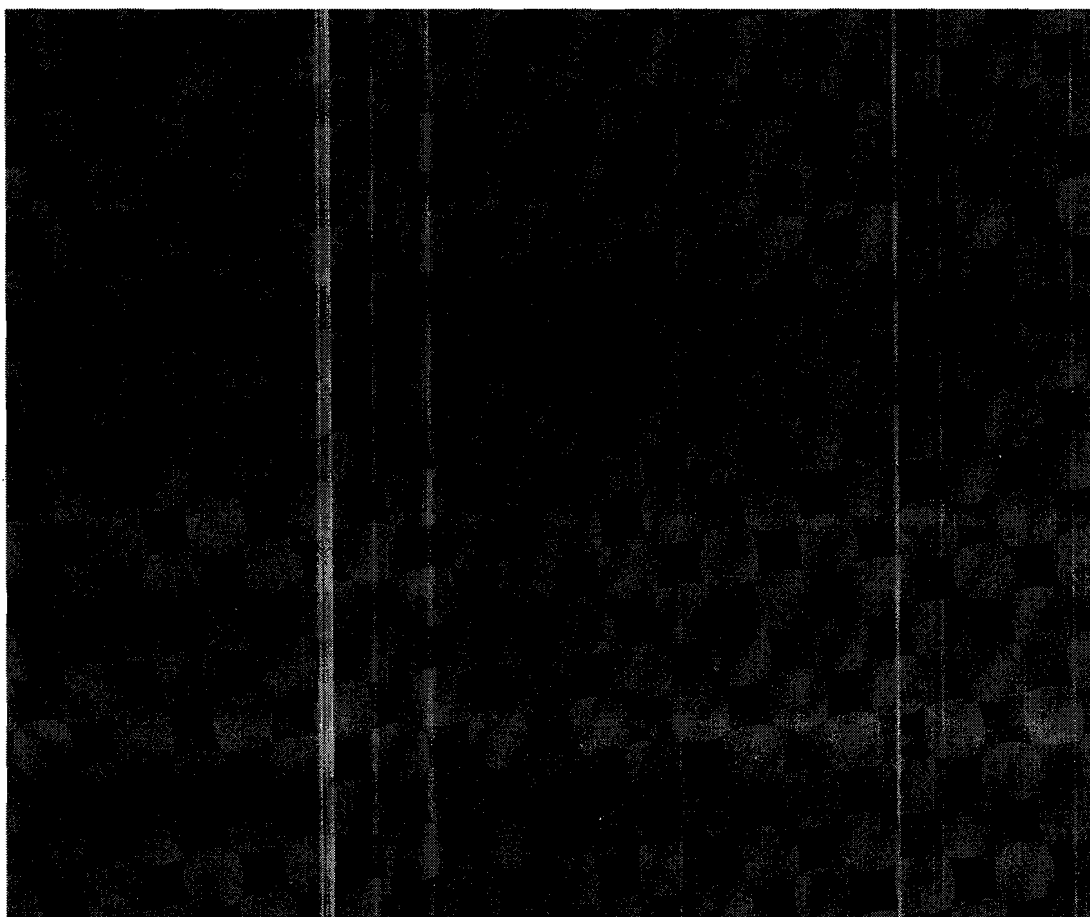
Kidney International 2003;64:1046-1049

FDA comment: the authors of this retrospective chart review reported that in patients receiving 650 ± 250 mL HES 450/0.7, GFR decreased ~ 7 mL/min more (estimated by the Cockcroft-Gault formula) at Day 3 and Day 5 in CABG patients than those who did not receive HES 450/0.7. The two arms were well matched at baseline except that intraoperative bypass time was 10 min longer in the HES arm ($p=0.01$). In addition to the possibility of residual confounding, use of the Cockcroft-Gault equation in this population needs to be validated. Most important of all, hetastarch was used in this study, not 6% HES 130/0.4, so caution is warranted before extrapolating these results to the current NDA.



J Clinical Anesthesia 2001;13:103-111

FDA comment: this small study (N=60) found no difference in levels of sensitive renal glomerular and tubular enzymes after administration of 15 mL/kg of lactated Ringer's solution or 2 *medium* (HES 200/0.5; HES 200/0.62) and 1 *high* MW (HES 450/0.7) HES solutions in healthy adults without pre-existing renal dysfunction undergoing elective ENT surgery.



(Mw 130; DS 0.4).

FDA comment: this review article is from Joachim Boldt, who has published widely in this field. Based on the data available in 2002, he advocated judicious use of *low* [sic] MW HES solutions (6% HES 130/0.4) in subjects with known renal dysfunction (defined as >3 mg/dL). The data contained in this NDA are reassuring but insufficient to fully address this important issue.



{Anesth Analg 2006;103:191-9}

FDA comment: this RCT (N=50) compared 5% human albumin vs. 6% HES 130/0.4 in subjects >70 y/o undergoing abdominal surgery. Levels of IL-6, sELAM-1, sICAM-1, creatinine clearance, α -GST, β -NAG, and α -1-microglobulin were lower in the 6% HES 130/0.4 treatment arm.

6.0 APPENDIX

Table 1: Clinical Trial Patient Demographics by Treatment Arm (Source: Sponsor)									
Treatment Arm	CTM	No of Subjects	Male N (%)	Female N (%)	Age Cohorts (years)				
					≤2	3-17	18-64	65-75	>75
HES 130/0.4	2% HES 130/0.4	51	20 (39.2)	31 (60.8)			46 (90.2)	5 (9.8)	
	4% HES 130/0.4	54	23 (42.6)	31 (57.4)			49 (90.7)	5 (9.3)	
	6% HES 130/0.4	471	313 (66.5)	158 (33.5)	41 (8.7)		281 (59.7)	118 (25.1)	31 (6.6)
	10% HES 130/0.4	204	133 (65.2)	71 (34.8)			157 (77.0)	33 (16.2)	14 (6.9)
	HES 130 TOTAL	768	477 (62.1)	291 (37.9)	41 (8.7)		521 (67.8)	161 (21.0)	45 (5.9)
Control	6% HES 200/0.5	297	180 (60.6)	117 (39.4)		1 (0.3)	199 (67.0)	86 (29.0)	11 (3.7)
	6% HES 450/0.7	51	34 (66.7)	17 (33.3)			32 (62.7)	11 (21.6)	8 (15.7)
	Normal saline	36	25 (69.4)	11 (30.6)			18 (50.0)	11 (30.6)	7 (19.4)
	Crystalloids	20	15 (75.0)	5 (25.0)			10 (50.0)	8 (40.0)	2 (10.0)
	Glucose	52	21 (40.4)	31 (59.6)			51 (98.1)	1 (1.9)	
	Albumin	41	25 (61.0)	16 (39.0)	41 (100.0)				
	Gelatin	50	44 (88.0)	6 (12.0)			15 (30.0)	20 (40.0)	15 (30.0)
	Control TOTAL	547	344 (62.9)	203 (37.1)	41 (7.5)	1 (0.2)	325 (59.4)	137 (25.0)	43 (7.9)
TOTAL		1315	821 (62.4)	494 (37.6)	82 (6.2)	1 (0.1)	846 (64.3)	298 (22.7)	88 (6.7)

Table 2. Hemorrhagic and other adverse events by Treatment Arm (Source: Sponsor)				
MedDRA System Organ Class	6% HES 130 N=447	HES 130 Total N=720	Controls N=547	Total Overall N=1267
Blood and lymphatic system disorders	22 (4.9)	24 (3.3)	13 (2.4)	37 (2.9)
Cardiac disorders	160 (35.8)	195 (27.1)	181 (33.1)	376 (29.7)
Metabolism & nutrition disorders	142 (31.8)	181 (25.1)	150 (27.4)	331 (26.1)
Musculoskeletal & connective tissue disorders	117 (26.2)	148 (20.6)	132 (24.1)	280 (22.1)
Nervous system disorders	74 (16.6)	107 (14.9)	91 (16.6)	198 (15.6)
Renal and urinary disorders	44 (9.8)	52 (7.2)	49 (9.0)	101 (8.0)
Respiratory, thoracic and medistinal disorders	69 (15.4)	85 (11.8)	71 (13.0)	156 (12.3)
Surgical and medical procedures	211 (47.2)	290 (40.3)	233 (42.6)	523 (41.3)
Vascular disorders (e.g., bleeding)	187 (41.8)	268 (37.2)	219 (40.0)	487 (38.4)

Median (Mean ± SD) (Source: Sponsor)						
Treatment Arm	CTM	No of Subjects	Duration of Exposure (h)	Treatment Days	Total Volume of Study Solution (mL)	Total Volume of Study Solution (mL/kg)
HES 130/0.4	2% HES 130/0.4	51	12.0 (12.0 ± 2.0)	6.0 (5.8 ± 0.6)	750 (750 ± 0)	60.0 (59.3 ± 11.7)
	4% HES 130/0.4	54	12.0 (11.4 ± 3.0)	6.0 (5.5 ± 1.3)	750 (757 ± 51)	58.8 (58.1 ± 18.2)
	6% HES 130/0.4	471	5.3 (16.0 ± 40.3)	1.0 (2.0 ± 2.2)	1250 (1346 ± 952)	25.6 (36.8 ± 56.9)
	10% HES 130/0.4	204	10.0 (11.5 ± 7.7)	7.0 (7.1 ± 3.1)	500 (603 ± 173)	62.5 (57.0 ± 26.7)
	HES 130 TOTAL	768	9.0 (14.5 ± 31.8)	2.0 (3.9 ± 3.3)	750 (1081 ± 822)	41.9 (45.7 ± 47.8)
Control	6% HES 200/0.5	297	7.4 (20.3 ± 63.2)	1.0 (4.0 ± 4.4)	1250 (1297 ± 807)	31.3 (48.1 ± 66.4)
	6% HES 450/0.7	51	2.6 (3.2 ± 1.8)	1.0 (1.0 ± 0)	1500 (1584 ± 958)	16.0 (19.6 ± 14.8)
	Normal saline	36	21.5 (19.2 ± 7.8)	7.0 (6.5 ± 1.8)	817 (781 ± 174)	75.7 (70.4 ± 26.2)
	Crystalloids	20	96.0 (96.9 ± 3.7)	5.0 (5.1 ± 0.2)	1300 (1289 ± 48)	80.3 (82.7 ± 11.3)
	Glucose	52	12.0 (12.0 ± 4.3)	6.0 (5.5 ± 1.2)	750 (750 ± 0)	60.0 (58.0 ± 16.8)
	Albumin	41	2.3 (3.5 ± 3.3)	1.0 (1.1 ± 0.4)	100 (114 ± 85)	16.2 (19.4 ± 12.7)
	Gelatin	50	8.4 (15.3 ± 22.6)	1.0 (1.4 P0.9)	1500 (1543 ± 591)	25.2 (27.8 ± 15.1)
	Control TOTAL	547	7.9 (19.0 ± 49.9)	1.0 (3.6 ± 3.7)	929 (1171 ± 787)	31.7 (45.1 ± 62.6)
TOTAL		1315				

Study (Source: Sponsor)			
Treatment	Phase 1 Studies Number of subjects (%)	Volume Replacement Studies Number of subjects (%)	Stroke & Sudden Hearing Loss Studies Number of subjects (%)
2% HES 130/0.4			51 (100)
4% HES 130/0.4			54 (100)
6% HES 130/0.4	43 (9.1)	355 (75.4)	73 (15.5)
10% HES 130/0.4	36 (17.6)		168 (82.4)
HES TOTAL	67 (8.7)	355 (46.2)	346 (45.1)
6% HES 200/0.5		208 (70.0)	89 (30.0)
6% HES 450/0.7		51 (100)	
Saline 0.9%			36 (100)
Crystalloids			20 (100)
Glucose			52 (100)
Albumin		41 (100)	
Gelatin		50 (100)	
CONTROLS TOTAL		350 (64.0)	197 (36.0)
TOTAL	67 (5.1)	705 (53.6)	543 (41.3)

Volume (mL)	HES 130/0.4 N=Number of Subjects (%)				Control Group N=Number of Subjects (%)				Total N=1315
	2%, 4% N=104	6% N=471	10% N=204	Total N=768	200/0.5 N=297	450/0.7 N=51	Crystalloid, Glucose, Albumin, Gelatin N=199	Total N=547	
≤ 1000	2 (2)	163 (35)	32 (16)	185 (24)	56 (19)	19 (37)	53 (26)	128 (23)	313 (24)
1000-2000	1 (1)	114 (24)	5 (3)	120 (16)	81 (27)	22 (43)	41 (20)	134 (25)	254 (19)
2000-3000	8 (8)	77 (16)	10 (5)	95 (12)	70 (24)	6 (12)	5 (3)	81 (15)	176 (13)
3000-4000	6 (6)	30 (6)	10 (5)	46 (6)	8 (3)	2 (4)	2 (2)	12 (2)	58 (4)
>4000	80 (80)	87 (19)	147 (72)	322 (42)	82 (28)	2 (4)	99 (49)	183 (34)	505 (38)

Table 2. Volume (mL/kg) of Fluids Administered (Sponsor)									
Volume mL/kg	HES 130/0.4 N=Number of Subjects (%)				Control Group N=Number of Subjects (%)				Total N=1315
	2%, 4% N=104	6% N=471	10% N=204	Total N=768	200/0.5 N=297	450/0.7 N=51	Crystalloid, Glucose, Albumin N=199	Total N=547	
≤10	2 (2)	110 (23)	28 (14)	116 (15)	45 (15)	9 (18)	18 (9)	72 (13)	188 (14)
>10-20	1 (1)	75 (16)	5 (3)	93 (12)	22 (7)	27 (53)	30 (15)	79 (14)	172 (13)
>20-30	3 (3)	89 (19)	4 (2)	96 (13)	65 (22)	7 (14)	24 (12)	93 (17)	168 (13)
>30-40	3 (3)	66 (14)	6 (3)	75 (10)	65 (22)	4 (8)	8 (4)	30 (6)	106 (8)
>40-50	16 (16)	46 (10)	14 (7)	76 (10)	17 (6)	2 (4)	11 (6)	30 (6)	106 (8)
>50	80 (80)	85 (18)	145 (71)	310 (40)	81 (27)	2 (4)	94 (47)	177 (32)	487 (37)
N/A			2 (1)	2 (0)	2 (1)			2 (0)	4 (0)

Study	Test Dosage	Control Dosage	Test: mL Infused	Control: mL Infused	Statistics	Secondary Endpoints
HS-13-13-DE 1 center	6% HES 130/0.4 ≤2500 mL	6% HES 200/0.5 ≤2500 mL	2019 ± 556	2188 ± 1050	Equivalence not shown (difference not clinically meaningful)	1FVIII and vWF in test group
HS-13-19-FR 4 centers	6% HES 130/0.4 ≤3000 mL	6% HES 200/0.5 ≤3000 mL	1960 ± 971	1928 ± 901	Equivalence shown	1FVIII in test group
HS-13-30-US 6 centers	6% HES 130/0.4 Unrestricted	6% HES 450/0.7 Unrestricted	1613 ± 778	1584 ± 958	Equivalence shown	No difference between groups
HS-13-14-NL 2 centers	6% HES 130/0.4 ≤3000 mL	6% HES 200/0.5 ≤3000 mL	2913 ± 779	2884 ± 1175	Equivalence not shown (difference not clinically meaningful)	1vWF in test group