1. Title Page

Study title	Prospective controlled double-blind phase III bicenter study on the efficacy and safety of a balanced gelatine solution in combination with a balanced electrolyte solution versus a standard gelatine solution in combination with a non-balanced electrolyte solution in patients scheduled for abdominal surgery
Name of test drug / Investigational Product	
Test product	Gelofusine® Balanced combined with Sterofundin® ISO
Reference product	Gelafundin® 4% combined with NaCl 0.9%
Indication studied	Male or female patients aged 18 to 90 years scheduled to undergo elective abdominal surgery with assumed intraoperative volume requirement of at least 15 mL/kg body weight (Broca) gelatine solution.
Study design	Prospective, controlled, randomized, double-blind, bicenter phase III study performed in 2 parallel groups.
Sponsor	B. Braun Melsungen AG Carl-Braun-Straße 1 34212 Melsungen, Germany
Study number	HC-G-H-0904
EudraCT number	2010-018524-58
Development phase of study	Phase III
Study initiation date	First patient in: 20.12.2011
Study completion date	Last patient out: 31.08.2012
Coordinating investigator (Leiter der klinischen Prüfung according to German Drug Law)	[redacted] Universitätsklinikum Aachen Pauwelsstraße 30 52074 Aachen

Study coordinator	[redacted] Senior Scientific Manager Clinical Development, CoE Pharmaceuticals B. Braun Melsungen AG Carl-Braun-Straße 1 34212 Melsungen, Germany
GCP	This study was performed in compliance with ICH Good Clinical Practice (CPMP/ICH/135/95).
Date of the synopsis	09.10.2015.

2. Synopsis

Name of sponsor	B. Braun Melsungen AG, Carl-Braun-Straße 1, 34212 Melsungen, Germany
Name of finished product	Gelofusine® Balanced
Name of active ingredients	Gelatine polysuccinate (=modified fluid gelatine), sodium chloride, sodium acetate trihydrate, potassium chloride, calcium chloride dehydrate, magnesium chloride hexahydrate
Study title	Prospective controlled double-blind phase III bicenter study on the efficacy and safety of a balanced gelatine solution in combination with a balanced electrolyte solution versus a standard gelatine solution in combination with a non-balanced electrolyte solution in patients scheduled for abdominal surgery
Investigators	▪ Coordinating Investigator : [redacted] Universitätsklinikum Aachen ▪ Principal Investigator Center 1 : [redacted] Universitätsklinikum Aachen ▪ Principal Investigator Center 2 : [redacted] Universitätsklinikum Frankfurt/ Main
Study centers	1. Klinik für Operative Intensivmedizin Universitätsklinikum Aachen Pauwelsstraße 30 52074 Aachen 2. Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie Universitätsklinikum Frankfurt/ Main Theodor-Stern-Kai 7 60590 Frankfurt/ Main
Publication (reference)	–
Study period	Date of first patient enrolled : 20.12.2011 Date of last patient completed : 31.08.2012
Phase of development	III
Objectives	Primary objective: The primary objective of the study was to assess the intraoperative change of the base excess and chloride after treatment of a balanced volume replacement regimen (balanced gelofusine solution combined with a balanced electrolyte solution) compared with a non-balanced volume replacement regimen (non-balanced gelatine solution combined with a non-balanced electrolyte solution) in adult patients undergoing elective abdominal surgery.

Objectives	Secondary objective: Secondary objectives were safety and efficacy of the two different volume replacement regimens expressed by parameters such as arterial blood gas analysis, coagulation status, renal function, requirements of blood products, adverse events, hemodynamics, IP administration, clinical outcome, demographic data, and surgery related data.
Methodology	Prospective, controlled, randomized, double-blind, bicenter phase III study performed in 2 parallel groups.
Number of patients	▪ All-Patients-Treated Set APTS : N=40 (balanced: 20, unbalanced: 20) ▪ Full Analysis Set FAS : N=39 ▪ Per Protocol Set PP : N=33
Diagnosis and main criteria for inclusion	Male or female patients aged 18 to 90 years scheduled to undergo elective abdominal surgery with assumed intraoperative volume requirement of at least 15 mL/kg body weight (Broca) gelatine solution.
Test product	Gelofusine® Balanced combined with Sterofundin® ISO
Dose	Individual volume replacement with target values of 10 mmHg ≤ CVP ≤ 14 mmHg minus PEEP after treatment with vasoactive agent and MAP > 65 mmHg
Mode of administration	Intravenous infusion
Batch no.	0105H91, 0176H91, 120157651, 114738143
Duration of treatment	During surgery and at ICU / IMC as needed
Reference product	Gelafundin® 4% combined with NaCl 0.9%
Dose	Individual volume replacement with target values of 10 mmHg ≤ CVP ≤ 14 mmHg minus PEEP after treatment with vasoactive agent and MAP > 65 mmHg
Mode of administration	Intravenous infusion
Batch no.	0173H91, 0186H91, 11432450, 114117651
Criteria for evaluation	
Efficacy	Changes from baseline to end of surgery in ▪ base excess (BE) ▪ chloride are the primary efficacy criteria. Secondary efficacy criteria ▪ changes from baseline to end of surgery in hemodynamic parameters ▪ changes from baseline to end of study in hemodynamic parameters ▪ the amount of IP administration intraoperative / postoperative / total measured in mL/kg bw/h and mL ▪ the complication rates during drug monitoring ▪ the incidence of relevant concomitant medication

Safety	▪ Arterial blood gas analysis ○ pondus hydrogenii (pH); not temperature corrected ○ Base excess (BE) [mmol/L] ○ Bicarbonate (HCO_3) [mmol/L] ○ Lactate [mmol/L] ○ Sodium (Na^+) [mmol/L] ○ Potassium (K^+) [mmol/L] ○ Calcium (Ca^{2+}) [mmol/L] ○ Chloride (Cl^-) [mmol/L] ○ Partial pressure of carbon dioxide (pCO_2) [mmHg] ○ Partial pressure of oxygen (pO_2) [mmHg] ○ Oxygen saturation (SaO_2) [%] ○ Hemoglobin (Hb) [g/dL] ○ Hematocrit (Hct) [%] ▪ Coagulation status ○ Antithrombin III (AT III) [%] ○ Fibrinogen [g/dL] ○ Platelet count (PC) [µ/L] ○ Activated partial thromboplastin time (aPTT) [s] ○ ROTEM (CT, MCF, LI 30) ○ Platelet aggregation (TRAPtest, ASPItest, ADPtest) – only site Frankfurt am Main ▪ Renal function ○ Serum creatinine (S_{Crea}) [mg/g] ○ Creatinine clearance [mL/min] ○ Blood urea nitrogen (BUN) [mg/dL] ○ Cystatin C [mg/L] ○ Amount of urine excreted (diuresis) ○ N-acetyl-beta-glucosaminidase (β-NAG) [units L^{-1}] ○ Neutrophil gelatinase-associated lipocalin (NGAL) [ng mL^{-1}] ○ Glomerular filtration rate (GFR) [mL/min] ▪ Requirement of blood products / drainage and estimated blood loss / secondary bleeding ▪ Time on ventilator ▪ Length of ICU / IMC stay ▪ (Serious) adverse events.
Statistical methods	▪ U test (Wilcoxon-Mann-Whitney) ▪ χ^2 test ▪ Wilcoxon test ▪ t-test ▪ Analysis of covariance with site as cofactor and baseline as covariate

Efficacy results

- Change from baseline in base excess in the surgery period [FAS]:
  - balanced treatment : –2.59 ± 2.25 (median: –2.65) mmol/L
  - unbalanced treatment: –4.79 ± 2.38 (median: –4.70) mmol/L

(U test: p=0.0117).

- Change from baseline in chloride in the surgery period [FAS]:
  - balanced treatment : 2.4 ± 1.9 (median: 3.0) mmol/L
  - unbalanced treatment: 5.2 ± 3.1 (median: 5.0) mmol/L

(U test: p=0.0045).

- Using α-adaption according to Bonferroni-Holm, the superiority of the balanced treatment was simultaneously shown for both primary endpoints.

- The superiority of the balanced treatment could be confirmed in the PP population (BE: p=0.0143; chloride: p=0.0071)

- At the end of the ICU / IMC period, a lower decrease of BE (FAS=PP: p=0.0044) and lower increase of chloride (FAS=PP: p=0.0010) upon balanced treatment was observed.

- No differences between both study sites with respect to the primary study outcomes were obtained.

- In the surgery period the following changes in hemodynamic parameters were observed:

Parameter	Balanced treatment			Unbalanced treatment			U test (p-value)
	mean	std	median	mean	std	median	
SAP [mmHg]	–9.4	35.0	–17.0	–9.4	26.9	–15.0	0.9368
DAP [mmHg]	–12.5	23.4	–16.0	–10.8	12.0	–12.0	0.4750
MAP [mmHg]	–11.5	26.6	–16.3	–10.4	15.6	–5.3	0.7755
HR [mmHg]	–3.1	15.6	2.0	6.5	18.5	2.0	0.3656
CVP [mmHg]	–3.5	6.1	–4.0	1.2	7.1	1.0	0.0260
PEEP [cmH_2O]	1.11	2.28	0.00	1.16	2.43	1.00	0.4923

A treatment difference was obtained for CVP which slightly decreased upon balanced and increased upon unbalanced treatment. This difference was not confirmed in the PP population (p=0.1002).

At the end of ICU / IMC stay no treatment differences with respect to hemodynamic parameters were detected.

- No statistically significant treatment differences with respect to the administered drug volume and rate of infusion were observed. During OP the following amount of drugs was used:

Parameter	Balanced treatment			Unbalanced treatment			U test (p-value)
	mean	std	median	mean	std	median	
Crystalloid component							
▪ volume [mL]	1353.7	714.4	1071.4	1519.4	1024.7	1170.8	1.0000
▪ inf. rate [mL/kg·h]	6.32	2.90	4.85	6.98	2.77	6.45	0.3201
Colloid component							
▪ volume [mL]	1513.8	726.7	1350.0	1619.0	724.5	1408.3	0.5740
▪ inf. rate [mL/kg·h]	7.22	3.03	6.75	7.81	3.07	7.35	0.5885

kg = kg (Broca)

Safety results

- Adverse events before first study drug administration were documented in
  - balanced treatment : N=10 (50.0%)
  - unbalanced treatment: N=12 (60.0%)

  patients. In the majority of patients Investigations (N=17), Blood and lymphatic system disorders (N=8), Vascular disorders (N=8), and Metabolism and nutrition disorders (N=7) were reported.

- Adverse events which occurred first after 1st study drug administration and before admission to ICU / IMC were documented in
  - balanced treatment : N=19 (95.0%)
  - unbalanced treatment: N=20 (100.0%)

  patients. The following system organ classes were concerned:

MedDRA SOC		Balanced [N=20]	Unbalanced [N=20]	χ^2 test (p-value)
All adverse events		19 (95.0%)	20 (100.0%)	0.3112
Blood	Blood and lymphatic system disorders	3 (15.0%)	4 (20.0%)	0.6773
Card	Cardiac disorders	2 (10.0%)	4 (20.0%)	0.3758
Genrl	General disorders and administration site conditions	1 (5.0%)	1 (5.0%)	1.0000
Inv	Investigations	18 (90.0%)	20 (100.0%)	0.1468
Metab	Metabolism and nutrition disorders	7 (35.0%)	9 (45.0%)	0.5186
Nerv	Nervous system disorders	–	2 (10.0%)	0.1468
Resp	Respiratory, thoracic and mediastinal disorders	1 (5.0%)	–	0.3112
Skin	Skin and subcutaneous tissue disorders	1 (5.0%)	–	0.3112
Vasc	Vascular disorders	15 (75.0%)	15 (75.0%)	1.0000

No statistically significant treatment differences were observed.

- Serious adverse events or events of severe intensity did not occur in the surgery period.

- Adverse events which occurred first after admission to ICU / IMC were reported in
  - balanced treatment : N=15/19 (78.9%)
  - unbalanced treatment: N=14/19 (73.7%)

  patients. The following SOCs were concerned:

MedDRA SOC		Balanced [N=19]	Unbalanced [N=19]	χ^2 test (p-value)
All adverse events		15 (78.9%)	14 (73.7%)	0.7028
Blood	Blood and lymphatic system disorders	3 (15.8%)	1 (5.3%)	0.2904
Card	Cardiac disorders	1 (5.3%)	1 (5.3%)	1.0000
Eye	Eye disorders	–	1 (5.3%)	0.3109
Gastr	Gastrointestinal disorders	5 (26.3%)	3 (15.8%)	0.4261
Genrl	General disorders and administration site conditions	1 (5.3%)	1 (5.3%)	1.0000
Inv	Investigations	11 (57.9%)	9 (47.4%)	0.5158
Metab	Metabolism and nutrition disorders	1 (5.3%)	1 (5.3%)	1.0000
Psych	Psychiatric disorders	–	1 (5.3%)	0.3109
Vasc	Vascular disorders	4 (21.1%)	3 (15.8%)	0.6756

- A serious adverse event of severe intensity occurred in one patient (Pat. ID 102/A102): increase CK (53680 U/L; probably due to ischaemia of both legs) after admission to ICU / IMC.

- Adverse events possibly related to the study medication were reported in
  - balanced treatment : N=15 (75.0%)
  - unbalanced treatment: N=15 (75.0%)

  patients. The following SOCs were concerned:

MedDRA SOC		Balanced [N=20]	Unbalanced [N=20]	χ^2 test (p-value)
All adverse events		15 (75.0%)	15 (75.0%)	1.0000
Blood	Blood and lymphatic system disorders	3 (15.0%)	1 (5.0%)	0.2918
Card	Cardiac disorders	–	1 (5.0%)	0.3112
Gastr	Gastrointestinal disorders	1 (5.0%)	1 (5.0%)	1.0000
Inv	Investigations	15 (75.0%)	13 (65.0%)	0.4902
Metab	Metabolism and nutrition disorders	1 (5.0%)	6 (30.0%)	0.0375
Skin	Skin and subcutaneous tissue disorders	1 (5.0%)	–	0.3112
Vasc	Vascular disorders	–	1 (5.0%)	0.3112

A higher rate of Metabolism and nutrition disorders was reported in the unbalanced treatment group (p=0.0375).

- No statistically significant treatment differences in the changes from baseline were observed at the end of surgery with respect to pH, lactate, Na^+, K^+, pCO_2, pO_2, SaO_2, Hb, Hct, anion gap, and strong ion deficit. HCO_3 showed a stronger decrease in the unbalanced treatment group (p=0.0157), and Ca^{2+} decreased – within the normal range – only in the unbalanced group (p=0.0001).

- No statistically significant treatment differences in the changes from baseline were observed at the end of ICU / IMC with respect to pH, lactate, Na^+, K^+, pCO_2, pO_2, SaO_2, Hb, Hct, and anion gap. HCO_3, Ca^{2+}, and strong ion deficit showed a stronger decrease in the unbalanced treatment group (p=0.0039, p=0.0002, and p=0.0143, resp.).

- No statistically significant treatment differences in the changes from baseline with respect to the coagulation status were observed except for ADP test which showed decreased values in the balanced treatment group (p=0.0553 at end of surgery, p=0.0323 at end of ICU / IMC stay).

- No statistically significant treatment differences in the changes from baseline with respect to the renal function were observed.

- No statistically significant treatment differences were observed with respect to blood loss during surgery and need of blood products.

Conclusions

The study demonstrated significantly smaller influences on blood gas analytic parameters, in the primary endpoints base excess and chloride, upon the balanced gelatine solution Gelofusine® Balanced combined with Sterofundin® ISO in comparison with the unbalanced gelatine solution Gelafundin® 4% combined with NaCl 0.9%.

No marked treatment differences were observed with respect to hemodynamics, coagulation, and renal function.

A comparable incidence and profile of adverse events was observed in both treatment groups. While the incidence of adverse events possibly related to the study medication was comparable in both treatment groups, the metabolism and nutrition disorders occurred in only one patient upon balanced but six patients upon unbalanced treatment.

3. Signature

The undersigned declare that they have read this revised synopsis and confirm that to the best of their knowledge it accurately describes the conduct and results of the study HC-G-H-0904.

Responsibility	Name	Date	Signature
[redacted]	[redacted] B. Braun Melsungen AG Carl-Braun-Straße 1 34212 Melsungen, Germany	[redacted]	[redacted]
[redacted]	[redacted] B. Braun Melsungen AG Carl-Braun-Straße 1 34212 Melsungen, Germany	[redacted]	[redacted]