Fakultät für Medizin

Klinikum rechts der Isar Technische Universität München

SUPERADD

SUbstition of PERioperative Albumin Deficiency Disorders

(Einfluss der Therapie einer perioperativen Hypoalbuminämie auf postoperative Komplikationen)

Clinical Trial

Test product: Human-Albumin 20 % Behring, salzarm Infusionslösung

Study Code: SUPERADD

EudraCT Number: 2016-001313-24

First Patient First Visit: 20.06.2017 – **Last Patient Last Visit:** 03.06.2020

Termination of Clinical Trial: 21.04.2021 (LPLV)

Sponsor
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Investigator (Sponsor Delegated Person)
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Synopsis

1.	**Sponsor:** Technische Universität München (TUM), Fakultät für Medizin Ismaninger Strasse 22, D- 81675 München, Germany **Sponsor Delegated Person (SDP):** Prof. Dr. Manfred Blobner
2.	**Name of Finished Product:** Human-Albumin 20 % Behring, salzarm Infusionslösung (Authorisation Number 10530a/96)
3.	**Name of Active Ingredient:** human albumin (ATC Code: B05A A01)
4.	**Individual Study Table:** (only required for submissions) n.a.
5.	**Study Title:** SUbstition of PERioperative Albumin Deficiency Disorders (Einfluss der Therapie einer perioperativen Hypoalbuminämie auf postoperative Komplikationen)
	Study Design: randomized, controlled, outcome-assessor blinded single centre
	Study (Protocol) Code Number: SUPERADD V4.1
	Eudra-CT Number: 2016-001313-24
6.	**Investigator(s):** Prof. Dr. Manfred Blobner, Prof. Dr. Stefan Schaller, Prof. Dr. Bettina Jungwirth, Dr. Kristina Fuest, Dr. Sebastian Schmid, Catherina Bubb
7.	**Participating Study Centre:** Klinikum rechts der Isar an der Technische Universität München Klinik für Anästhesiologie und Intensivmedizin Ismaninger Straße 22 D- 81675 München, Germany The study was planned and conducted as a single-centre study.
8.	**Publication:** not published yet

9.	**Study period:** First patient first visit (FPFV): 20.06.2017; Last patient out: 03.06.2020 Study ended with 600 patients randomized as per study protocol.
	Approvals and Amendments **Approval**: Bundesinstitut für Arzneimittel und Medizinprodukte (PEI): 13.02.2017; Ethics Committee (EC): 02.06.2017 **Amendment 1**: The following major changes were included in AM 1: 1. *Number of patients after interim analysis* 2. *Secondary endpoints* 3. *Minor changes* Approval AM1: PEI: 16.10.2018; EC: 09.10.2018, CSP Version 4.1, 08.08.2018
10.	**Phase of development** Phase IV
11.	**Objectives:** **Primary Objective:** Reduction of postoperative complications of either high-risk surgical procedures or high-risk surgical patients through perioperative therapy of hypoalbuminemia (defined as < 30 g/L). **Secondary Objectives:** Amelioration of the prespecified secondary outcomes of either high-risk surgical procedures or high-risk surgical patients through perioperative therapy of hypoalbuminemia (defined as <30g/l).

12.	**Methodology** SuperAdd is a single-centre, prospective, randomized, outcome-assessor blinded, patient blinded controlled trial. The primary outcome was the frequency of postoperative complications identified using the Postoperative Morbidity Survey graded ≥ 2 according to the Clavien-Dindo Score. Adult patients at risk to develop hypalbuminaemia, i.e., ASA III or IV or high-risk surgery, were recruited after written informed consent was obtained. The albumin concentration was assessed before the induction of anaesthesia and every 3 h until admission to the postanaesthesia care unit. If albumin concentrations dropped below 30 g/L, patients were randomly allocated to the control or the treatment group. The study intervention was a goal-directed human albumin substitution aimed at a concentration > 30 g/L during surgery and postanaesthesia care unit stay. The patients in the control group are treated according to standard clinical care. Postoperative visits are to be performed on days 1, 3, 5, 8, and 15, as well as by telephone 6 months after surgery.
13.	**Sample size (planned/analysed):** Planned: 600 patients Included / analysed: 600 / 592 patients
14.	**Patient Population (Diagnosis):** Adult elective surgical patients at risk to develop hypalbuminaemia, i.e., ASA III or IV or high-risk surgery. ITT population (all patients correctly randomized with serum albumin < 30 g/L) was used for the primary analysis. Safety cohort was all patients who have been randomized.
	Main criteria for inclusion 1. patients older than 18 years 2. patients, who voluntarily signed the consent form of the study 3. a. ASA III or IV OR b. planned high risk surgery: open aortic surgery, open revascularization of lower limbs, esophagectomy, cystectomy, pancreatic surgery, hepatic surgery, thrombectomy/embolectomy, amputation of a limb, replacement of artificial hip or knee joint

15.	**Test product, dose and mode of administration** **Study treatment:** goal-directed albumin therapy, i.e., treatment of hypalbuminaemia < 30< g/L with Human-Albumin 20 % Behring, salzarm Infusionslösung, solution for injection, CSL-Behring **Batch-No. (Ch.-B):** - K9544411A - K9644411B - K9644411A - M1844411A - P100064153 Authorisation Number 10530a/96
16.	**Duration of administration** Till PACU (post anesthesia care unit) discharge
17.	**Background therapy:** standard of care, i.e., treatment of hypalbuminaemia only if serum albumin < 20 g/L and clinically necessary **Comparator:** Human-Albumin 20 % Behring, salzarm Infusionslösung, solution for injection, CSL-Behring
	Blinding: Patient and outcome-assessor blinded

18.	**Criteria for evaluation:** **Primary endpoint:** Postoperative Complications assessed by POMS (Postoperative Morbidity Survey) and Clavien-Dindo-Score till day 15. **Secondary questions:** 1. subjective quality of recovery 2. in-hospital mortality 3. 180-day mortality 4. length of stay in the PACU, intensive care unit and hospital 5. incidence of complications and the respective surrogate variables in the nine POMS domains (e.g., acute kidney injury, pulmonary congestion, myocardial injury after noncardiac surgery, perioperative catecholamine requirements, hypotension, infusion, and transfusion) 6. clavien dindo score till hospital discharge 7. applied infusion volume 8. applied catecholamines 9. applied red packed cells 10. applied platelets concentrates 11. applied coagulation factors 12. frequency and duration of hypotension 13. efficiency of the albumin substitution
	Efficacy: The primary outcome measure is the occurrence and severity of postoperative complications, identified using the Postoperative Morbidity Survey (POMS) assessed on postoperative days 3, 5, 8, and 15, and graded according to the Clavien-Dindo Score. In brief, the POMS counts the number of domains, in which a complication leading to a prolongation of hospitalization occurs. The nine screened domains are pulmonary, infectious, cardiovascular, neurological, renal, gastrointestinal, wound, pain, and hematological morbidities. Since the POMS does not grade the severity of each complication, we additionally grade each complication using the Clavien and Dindo scale (Table 1). The primary endpoint is the frequency of patients with at least one clinically relevant postoperative complication, graded as Clavien-Dindo Score ≥ 2, on at least one postoperative day until day 15.

	Safety assessments Safety assessment was done in 600 patients randomized until hospital discharge according to POMS and Clavien-Dindo as for the primary outcomes.
19.	**Statistical methods:** All analyses were prespecified in the statistical analysis plan, which was published publicly at the trial website www.superadd.de. The primary endpoint was the incidence of any postoperative complications graded as Clavien-Dindo ≥ 2. The two treatment groups were compared using a two-sided chi-2-test for independent samples regarding the incidence of any postoperative complication. The results were presented as absolute risk reduction based on the Mantel–Haenszel risk differences and its improved confidence interval estimate. Sub-groups analyses and adjustments were included for risk groups according to ASA status, preoperatively existing vs. intraoperatively acquired hypalbuminemia, and varying surgical interventions. Exploratory comparisons were performed of each component of the Clavien-Dindo, as well as each domain of the POMS. Scaled surrogate variables of fluid therapy, such as creatinine concentration, vasopressor infusion rates, or need for supplementary oxygen during PACU, were compared with either t-tests or Mann-Whitney-U tests, according to the distribution of the variable. Statistical significance was assumed at an alpha level of 0.05. Statistical analyses were conducted using Statistical Package for the Social Sciences 27.0 (IBM SPSS Statistics, Chicago, IL, USA). The sample size was, as defined prospectively, recalculated by an independent statistician of the data safety and monitoring board comparing the two treatment groups for the incidence of any postoperative complications graded as Clavien-Dindo ≥ 2 and > 2, using a two-sided chi-2-test for independent samples. Based on the interim analysis, the maximum sample size of 300 patients per group was determined, as described in detail previously.

20.

Summary - Conclusions:

Patient demographics and patient disposition

Tab 1. Pre– and Intraoperative Characteristics of Patients.*

Characteristics	Intervention (N = 295)	Standard (N = 297)
Age (IQR) – year	70 (61 – 77)	69 (60 – 76)
Weight (IQR) – kg	74 (62 – 83)	75 (64 – 84)
Body mass index (IQR) – kg/m²	24.9 (21.6 – 28)	24.8 (22 – 27.8)
Female sex – no. (%)	122 (41.4)	118 (39.7)
Medical History		
Renal function		
Creatinine clearance ≥ 90 ml/min – no. (%) †	222 (75.3)	225 (75.8)
Creatinine clearance 60 – 90 ml/min – no. (%)	41 (13.9)	52 (17.5)
Creatinine clearance 30 – 60 ml/min – no. (%)	28 (9.5)	18 (6.1)
Creatinine clearance 15 – 30 ml/min – no. (%)	4 (1.4)	2 (0.7)
Creatinine clearance < 15 ml/min / dialysis – no.	0	0
History of myocardial infarction – no. (%)	54 (18.3)	51 (17.2)
High–sensitive troponin T (IQR) – ng/l	13 (7 – 22)	13 (8 – 19)
Immature platelet fraction (IQR) – %	2.2 (1.4 – 3.5)	2.5 (1.6 – 3.6)
Heart failure – New York Heart Association (NYHA)		
NYHA I – no. (%)	52 (17.6)	50 (16.8)
NYHA II – no. (%)	89 (30.2)	87 (29.3)
NYHA III–IV – no. (%)	36 (12.2)	34 (11.4)
History of cardiac arrhythmia or heart block – no. (%)	78 (26.4)	91 (30.6)
Mean arterial pressure (IQR) – mmHg	100 (93 – 108)	101 (92 – 110)
Heart rate (IQR) – beats/min	75 (65 – 86)	72 (63 – 82)
History of peripheral arterial disease – no. (%)	46 (15.6)	54 (18.2)
History of cerebrovascular insufficiency – no. (%)	31 (10.5)	21 (7.1)
History of dementia – no. (%)	1 (0.3)	0
Oxygen saturation at room air (IQR) – %	95 (93 – 97)	95 (94 – 96)
Chronic lung disease		
compensated – no. (%)	66 (22.4)	60 (20.2)
need for oxygen – no. (%)	9 (3.1)	4 (1.3)
History of collagenosis – no. (%)	3 (1.0)	10 (3.4)
History of gastrointestinal disease – no. (%)	201 (68.1)	180 (60.6)
History of liver diseases (Child–Pugh)		
Child A – no. (%)	54 (18.3)	49 (16.5)
Child B – no. (%)	5 (1.7)	5 (1.6)
Fasting glucose (IQR) – mg/dl	115 (94 – 133)	113 (96 – 135)
Drug–treated diabetes mellitus – no. (%)	62 (21.0)	51 (17.2)
History of neurologic disease		
without residuals – no. (%)	26 (8.8)	24 (8.1)
with residuals – no. (%)	31 (10.5)	34 (11.4)
History of solid cancer – no. (%)	185 (62.7)	157 (52.9)
History of lymphoma – no. (%)	5 (1.7)	9 (3.0)
History of leukemia – no. (%)	1 (0.3)	1 (0.3)
Acquired immune deficiency syndrome (AIDS) – no.	0	0
Transplanted organs – no. (%)	4 (1.4)	3 (1.0)
History of alcohol abuse – no. (%)	62 (21.0)	65 (21.9)
Preoperative hemoglobin concentration (IQR) – g/dl	11.0 (9.3 – 12.4)	11.4 (9.7 – 12.7)
Preoperative C–reactive protein (IQR) – mg/l ‡	14 (2 – 52)	5 (3 – 28)
Surgical and anesthesia data		
Surgical procedure ‡		
minor vascular – no. (%)	10 (3.4)	22 (7.4)
major vascular – no. (%)	44 (14.9)	48 (16.2)
minor visceral – no. (%)	21 (7.1)	11 (3.7)
major visceral – no. (%)	126 (42.7)	122 (41.1)
thoracic – no. (%)	20 (6.8)	9 (3.0)
minor hepatic – no. (%)	0	2 (0.7)
major hepatic – no. (%)	16 (5.4)	13 (4.4)
other orthopedic – no. (%)	43 (14.6)	52 (17.5)
orthopedic trauma – no. (%)	5 (1.7)	4 (1.3)
arthroplasty and spine – no. (%)	10 (3.4)	12 (4.0)
multiple trauma related – no. (%)	0	2 (0.7)
Estimated blood loss (IQR) – ml	800 (500 – 1500)	900 (500 – 1500)
Duration of surgery (IQR) – min	242 (151 – 371)	242 (140 – 347)
Duration of anesthesia (IQR) – min	346 (246 – 477)	334 (232 – 453)
Anesthetic technique		
general	226 (76.6)	232 (78.1)
regional	3 (1.0)	1 (0.3)
combined	65 (22.0)	64 (21.5)
Duration of anesthesia (IQR) – min	346 (246 – 477)	334 (232 – 453)
Surgical APGAR (IQR) – points	5 (4 – 7)	6 (5 – 7)
Risk Scores		
ASA–risk score (IQR) – points	3 (3 – 3)	3 (3 – 3)
Charlson comorbidity index (IQR) – points ‡	6 (3 – 10)	4 (2 – 10)
POSPOM (IQR) – points ‡	32 (28 – 36)	31 (26 – 35)

* Metric and ordinal characteristics are given as medians and interquartile range (IQR), as none is normally distributed by definition or after testing (Shapiro–Wilk test).

† The serum creatinine concentration of patients without a history of kidney disease or relevant symptoms is not determined. They are assigned to the patient cohort with a creatinine clearance of ≥ 90 ml/min.

‡ Unequal distribution of a characteristic between the two treatment groups is assumed if correlation coefficient > 0.1 (i.e., the χ value for nominal and the z value for metric or ordinal variables divided by the root of total number of patients > 0.1).[27]

Compliance:

There were six violations of inclusion and exclusion criteria. Four patient was randomized although the BMI was too high, another patient was included although he was also in another clinical trial and another patient was randomized although he has been randomized before in SUPERADD. The patient who was randomized a second time was randomized on 07.11.2017 and again randomized in another hospital stay 04.01.2018, i.e., after the completion of the data collection of the primary endpoint. It was decided that all these patients are to be excluded.

Two patients were excluded from the study since their laboratory albumin value which resulted in randomization was biased; their correct values were always above 3 g/L.

In total 8 patients were excluded in the primary analysis but not the safety analysis provided.

Protocol Violation (PV):

In total (including the above ones), PVs were reported in 28/598 patients: 6 PV were rated as major (inclusion/exclusion criteria). 16 PVs were using a human albumin 20% solution from another manufacturer than CSL-Behring, 4 patients in the control group received human albumin above 2.0 g/L serum albumin value, 1 patient in the intervention group was treated as being in the control group and in one patient a wrong patient ID number was entered in the randomization system.

Safety Results

Adverse Events:

	Intervention (n = 300)	Control (n = 300)	p-value
Pulmonary Complications	153	152	0.94
Infectious Complications	137	139	0.87
Renal Complications	62	60	0.84
Gastrointestinal complications	152	143	0.46
Cardio-vascular complications	72	78	0.57
Neurologic complications	52	37	0.09
Wound complications	99	93	0.60
Hematologic complications	101	99	0.86
Pain complications	122	110	0.31

SAEs:

	Intervention (n = 300)	Control (n = 300)	p-value
SAEs	15	6	0.046
SAE mortality	14	6	0.069

Mortality

	Intervention (n = 300)	Control (n = 300)	
In-hospital mortality	16	7	0.06
180-day mortality	52	36	0.07

Efficacy Results

Table 2. Primary and secondary Outcomes*

Outcome	Intervention (N = 295)	Standard (N = 297)	Risk difference (%) median difference (95% CI)
Primary outcome			
Any complication CDC ≥ Grade II †	250 (84.7)	259 (87.2)	–2.5 (–8.1 to 3.2) – p=0.39
Pulmonary complication CDC ≥ Grade II	149 (50.5)	149 (50.2)	
Infection CDC ≥ Grade II	132 (44.7)	133 (44.8)	
Renal complication CDC ≥ Grade II	55 (18.6)	58 (19.5)	
Gastro–intestinal complication CDC ≥ Grade II	148 (50.2)	141 (47.5)	
Cardio–vascular complication CDC ≥ Grade II	68 (23.1)	76 (25.6)	
Neurological complication CDC ≥ Grade II	48 (16.3)	34 (11.4)	
Wound complication CDC ≥ Grade II	91 (30.8)	84 (28.3)	
Hematological complication CDC ≥ Grade II	98 (33.2)	94 (31.6)	
Pain CDC ≥ Grade II	118 (40.0)	107 (36.0)	
Secondary outcome after randomization			
Hypotension (≥ 30% of baseline MAP)	199 (67.5)	199 (67.0)	0.5 (–7.1 to 8.0)
Median duration of hypotension – min (IQR) §	149 (32 – 480)	190 (61 – 542)	
Gelatin 4% treatment	119 (40.3)	129 (43.4)	–3.1 (–11.0 to 4.8)
Median infused gelatin solution – ml (IQR) §	442 (165 – 876)	500 (222 – 868)	
Albumin treatment	294 (99.7)	54 (18.2)	82 (76 to 86)
Median infused albumin – g (IQR) §	60 (40 – 80)	40 (40 – 80)	
Median S–albumin after treatment – mg/l (IQR)	34 (32 – 37)	26 (23 – 28)	9 (8 to 9)
Median infused Ringer acetate – l (IQR)	2.4 (0.8 – 3.8)	2.7 (0.8 – 4.0)	–0.1 (–0.4 to 0.1)
Noradrenalin treatment	176 (59.7)	160 (53.9)	5.8 (–2.2 to 13.7)
Median noradrenalin dose – µg/kg (IQR)	10 (4 – 24)	12 (4 – 36)	
Duration of noradrenalin treatment (min) §	180 (92 – 420)	207 (91 – 654)	
Erythrocyte transfusion	146 (49.5)	117 (39.4)	10.1 (2.1 to 17.9)
Platelet transfusion	14 (4.7)	3 (1.0)	3.7 (1 to 6.9)
Coagulation factor treatment ¶	77 (26.1)	54 (18.2)	7.9 (1.2 to 14.5)
Length of PACU stay – h (IQR)	15.4 (5.9 – 18.8)	15.8 (4.6 – 18.6)	0.3 (–0.6 to 1.2)
Acute kidney injury (AKIN) ≥ 1	143 (48.5)	173 (58.2)	–9.8 (–17.6 to –1.7)
AKIN 1	111 (37.6)	126 (42.4)	
AKIN 2	22 (7.5)	37 (12.5)	
AKIN 3	10 (3.4)	10 (3.4)	
New prescription of diuretics during PACU	18 (6.1)	38 (12.8)	–6.8 (–11.6 to –2.0)
Any complication CDC ≥ Grade IIIa	121 (41.0)	121 (40.7)	0.3 (–7.6 to 8.1)
Any complication CDC ≥ Grade IVa – ICU stay	52 (17.6)	55 (18.5)	–0.9 (–7.1 to 5.3)
Length of ICU stay – h (IQR) §	52 (32 – 119)	77 (32 – 260)	
Length of hospital stay – days (IQR)	5.4 (3.6 – 8.8)	5.2 (3.6 – 9.2)	0.0 (–0.4 to 0.6)
Any complication CDC = Grade V – Mortality	7 (2.4)	0 (0.0)	2.4 (0.6 to 4.8)
Hospital mortality	16 (5,4)	7 (2,4)	3,1 (–0,1 to 6,5)
6–month mortality	52 (17.6)	36 (12.1)	5.5 (–0.2 to 11.3)
Quality–of–Recovery (IQR) ‖			
Postoperatively day 1 (n=285 / n=277)	12 (10 – 14)	12 (10 – 14)	0 (0 to 1)
Postoperatively day 3 (n=275 / n=262)	14 (12 – 16)	14 (12 – 16)	0 (0 to 1)
Postoperatively month 6 (n=217 / n=206)	15 (13 – 17)	15 (13 – 16)	0 (0 to 0)

* Metric and ordinal characteristics are given as medians and interquartile range (IQR), as none is normally distributed by definition or after testing (Shapiro–Wilk test).
Data regarding the listed primary and secondary outcomes were censored on the 15th postoperative day unless otherwise stated. Exploratory outcomes are described in the Supplementary Appendix.

† All postoperative complications are graded according to the Clavien Dindo Classification (CDC)[20]

§ Only data from patients who received the treatment described in the respective line above are reported.

¶ Treatments were infusion of fibrinogen, prothrombin complex concentrate, or fresh frozen plasma.

‖ The Quality–of–Recovery score was obtained in the German translation of its 9–item version.[28]

	Overall Conclusion: Goal-directed perioperative albumin substitution in high-risk surgical patients or high-risk surgery did not reduce postoperative complications.

21.	**Date of report: 22.02.2021** **Date:** 22.02.2021 **Signature:** _____ SDP