Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Application Type	Original Application
STN	125644/0
CBER Received Date	December 9, 2016
PDUFA Goal Date	December 9, 2017
Division / Office	DBCD /OBRR
Priority Review	No
Reviewer Name(s)	Charles M. Maplethorpe M.D., Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Bio Products Laboratory
Established Name	Human Albumin Solution (HAS) 5% and 25%
(Proposed) Trade Name	ALBUMINEX
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	(b) (4) caprylate (b) (4) and N-acetyltryptophanate are used as stabilizers
Dosage Form(s) and Route(s) of Administration	intravenous
Dosing Regimen	
Indication(s) and Intended Population(s)	Hypovolemia, Ascites, Burns, Nephrotic syndrome, Acute Respiratory Distress Syndrome (ARDS), Cardiopulmonary Bypass
Orphan Designated (Yes/No)	No

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1. Executive Summary

Bio Products Laboratory has submitted STN 125644 for their Albumin (Human) product, Albuminex®. Albuminex is plasma-derived human albumin prepared in 5% and 25% solutions.

The following table compares the composition of the Albumin (Human) products manufactured by BPL:

Comparison of key specification parameters for various BPL's albumin (human) Products

	Zenalb® 4.5	**Zenalb® 20**	**Albumin (Human) 5%**	**Albumin (Human) 25%**
Active ingredient				
Albumin g/L	45	200	50	250
In-active ingredient				
Sodium (mmol/L)	100-160	50-120	130 -160	130 -160
Potassium (mmol/g of protein)	(b) (4)	(b) (4)	Not greater than 2	Not greater than 2
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4) caprylate (b) (4) (mmol/L)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4) acetyltryptophanate (mmol/L)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Aluminium (µg/L)	No more than 200	No more than 200	No more than 200	No more than 200

Source: STN125655/0 Clinical Overview, p. 12

The following indications (from the proposed package insert) are sought for Albuminex 5%:

1.1 Hypovolemia

ALBUMINEX 5% is indicated for restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate e.g. hypovolemia following shock due to trauma or sepsis, in surgical patients and in other similar conditions with volume deficiency when restoration and maintenance of circulating blood volume is required in both adult and pediatric patients. In pediatric patients to reverse hypovolemia and achieve normal capillary refill time.

1.2 Ascites

ALBUMINEX 5% is indicated for prevention of central volume depletion and maintenance of cardiovascular function after large volume parencentesis in patients with liver cirrhosis or other chronic liver disease in adults and children. ALBUMINEX 5% infusion plus administration of vasoactive drugs is indicated in the treatment of type I hepatorenal syndrome.

For patients with spontaneous bacterial peritonitis ALBUMINEX 5% is indicated as adjuvant treatment to antibiotic therapy.

1.3 Burns

ALBUMINEX 5% is indicated in patients with severe burn injury (> 20% total body surface area), but not until at least 12 to 24 hours after the burn, in order to correct protein loss, decrease overall fluid requirements, decrease systemic edema and stabilize cardiovascular hemodynamics without fluid overload (initial resuscitation should be with crystalloids).

1.4 Nephrotic syndrome

ALBUMINEX 5% is indicated in patients with nephrotic syndrome in combination with loop diuretics to reinforce the diuretic therapeutic effect, which is reduced by hypoalbuminemia, and for the correction of reduced oncotic pressure.

1.5 Acute Respiratory Distress Syndrome (ARDS)

ALBUMINEX 5% is indicated in conjunction with diuretics to correct fluid volume overload associated with ARDS.

1.6 Cardiopulmonary Bypass

ALBUMINEX 5% is indicated in cardiopulmonary bypass procedures as part of the priming fluids to passivate the synthetic surfaces of the extracorporeal circuit and maintain the patient's colloid oncotic pressure.

The following indications (from the proposed package insert) are sought for Albuminex 25%:

1.1 Hypovolemia

ALBUMINEX 25% is indicated for restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate e.g. hypovolemia following shock due to trauma or sepsis, in surgical patients and in other similar conditions with volume deficiency when restoration and maintenance of circulating blood volume is required in both adult and pediatric patients. In pediatric patients to reverse hypovolemia and achieve normal capillary refill time.

1.2 Ascites

ALBUMINEX 25% is indicated for prevention of central volume depletion and maintenance of cardiovascular function after large volume parencentesis in patients with liver cirrhosis or other chronic liver disease in adults and children. ALBUMINEX 25% infusion plus administration of vasoactive drugs is indicated in the treatment of type I hepatorenal syndrome.

For patients with spontaneous bacterial peritonitis ALBUMINEX 25% is indicated as adjuvant treatment to antibiotic therapy.

1.3 Burns

ALBUMINEX 25% is indicated in patients with severe burn injury (> 20% total body surface area), but not until at least 12 to 24 hours after the burn, in order to correct protein loss, decrease overall fluid requirements, decrease systemic edema and stabilize cardiovascular hemodynamics without fluid overload (initial resuscitation should be with crystalloids).

1.4 Nephrotic syndrome

ALBUMINEX 25% is indicated in patients with nephrotic syndrome in combination with loop diuretics to reinforce the diuretic therapeutic effect, which is reduced by hypoalbuminemia, and for the correction of reduced oncotic pressure.

1.5 Acute Respiratory Distress Syndrome (ARDS)

ALBUMINEX 25% is indicated in conjunction with diuretics to correct fluid volume overload associated with ARDS.

1.6 Cardiopulmonary Bypass

ALBUMINEX 25% is indicated in cardiopulmonary bypass procedures as part of the priming fluids to passivate the synthetic surfaces of the extracorporeal circuit and maintain the patient's colloid oncotic pressure.

A pre-BLA meeting was held on April 30, 2014, at which it was decided that the clinical basis for licensure could be based on the submission of a review of the medical literature for the use of Albumin (Human), irrespective of the product that was used. Accordingly, there are no clinical or pharmacokinetic/pharmacodynamic data for the use of Albuminex in STN 125644. See Appendix 1 for minutes of this meeting.

The literature that was reviewed to support the licensure of Albuminex is summarized in the following tables that were submitted by the applicant:

Appendix 2. Hypovolemia following Shock due to Trauma or Sepsis: Summary of Key RCTs

APPENDIX 3. ALBUMIN USE IN CHILDREN WITH MALARIA: SUMMARY OF KEY RCTS

Appendix 4. Table 4A and Table 4B
Table 4A: Hypovolemia post-surgery (cardiac / non-cardiac): Summary of key RCTs in adult patients
Table 4B: Hypovolemia post-surgery (cardiac / non-cardiac): Summary of key RCTs in pediatric patients

Appendix 5. Table 5 Tables 5A and 5B
Table 5A: Use of albumin solutions as priming solutions for cardiopulmonary bypass in adult patients
Table 5B: Use of albumin solutions as priming solutions for cardiopulmonary bypass in pediatric patients

Appendix 6. Hypovolemia in burn patients: Summary of key clinical studies

Appendix 7. Albumin in the treatment of patients with liver cirrhosis and its complications: Summary of key clinical trials

Appendix 8. Albumin in nephrotic syndrome: Summary of key clinical studies
Appendix 9. Albumin in acute respiratory distress syndrome: Summary of key clinical studies
Appendix 10. Meta-analyses and systematic reviews conducted for colloids vs crystalloids vs controls for hypovolemia post shock / trauma, post surgery and in burn patients
Appendix 11. RCTs with specific laboratory measurements related to safety

Pediatric Research Equity Act (PREA)

STN 125644 has been granted a full waiver under PREA because the studies would be impossible or highly impractical. A similar full waiver has been granted previously to other Albumin (Human) products. The full waiver was discussed at the May 31, 2014, Pediatrics Research Committee (PeRC) meeting.

From the minutes of the May 31, 2017, PeRC meeting on STN125644:

> **Albumin (Human) 5% and 25% Full Waiver (with an Agreed iPSP)**
> - Proposed indication: Treatment of Hypovolemia, Ascites, Burns, Nephrotic Syndrome, Acute Respiratory Distress Syndrome, Cardiopulmonary Bypass
> - The PREA trigger is new active ingredient with a PDUFA date of December 9, 2017.
> - The sponsor clarifies that there are no changes in the agreed upon iPSP. There is no clinical adult data for this product and it is approved based on CMC review only. The division is treating this product indication as a class.
> - The division clarified that labeling in Section 8.4 of Pediatric Use will indicate that studies have not been conducted in pediatric patients.
> - The PeRC agreed to full waiver, as described in the agreed iPSP.
>
> - *PeRC Recommendations*:
> - The PeRC concurs with the division to grant a full waiver because the studies are impossible or highly impractical.
> - The PeRC reviewed the proposed information for inclusion in the Pediatric Use section, and suggested that the review division should consider updating class labeling for albumin products based on published literature and the time and extent of use for albumin products in the pediatric population.

Recommendation.

STN 125644 may be approved because the applicant has submitted the required review of the medical literature that was determined to be the level of evidence required at the April 30, 2014, pre-BLA meeting. After STN 125644 was submitted, other review disciplines have identified deficiencies that are causing a Complete Response (CR) letter to be issued; these deficiencies do not impact the clinical review of this submission.

Labeling remains to be finalized. This will be done when the response to the CR letter is received.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic analysis was not submitted.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hypovolemia, Ascites, Burns, Nephrotic syndrome, Acute Respiratory Distress Syndrome (ARDS), Cardiopulmonary Bypass

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There are several licensed Albumin (Human) products.

2.3 Safety and Efficacy of Pharmacologically Related Products

This is discussed in the submission (see Appendices 2 -11). Information from other products is the basis for approval.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Not submitted

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

See Appendix 1 for minutes of the April 30, 2014, pre-BLA meeting at which it was decided that a review of the medical literature would suffice for licensure of Albuminex.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission consisted of a review of publication on the use of Albumin (Human). The review was adequate.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Not Applicable

3.3 Financial Disclosures

Not Applicable

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The CMC and facilities reviewers have recommended that STN 125644/0 receive a Complete Response (CR) letter based on inadequacies documented in the respective review memos.

5. Sources of Clinical Data and Other Information Considered in the Review

5.3 Table of Studies/Clinical Trials

See appendices 2 through 11 for tables of the clinical studies reviewed by the sponsor to support approval.

9.1.3 Pediatric Use and PREA Considerations

Pediatric studies have been waived because full waiver because the studies are impossible or highly impractical, as agreed by the May 31, 2017, PeRC.

10. Conclusions

STN 125644/0 may be approved.

11. Risk-Benefit Considerations and Recommendations

11.2 Risk-Benefit Summary and Assessment

The benefit exceeds the associated risks for the labeled indications.

11.3 Discussion of Regulatory Options

The decision to approve this application on the basis of a literature review of the use of Albumin (Human) was made at the April 30, 2014, pre-BLA meeting CRMTS #9311 (see Appendix 1).

11.4 Recommendations on Regulatory Actions

STN 125644 may be approved from a clinical review perspective.

11.5 Labeling Review and Recommendations

The final labeling review will commence when the response to the CR letter is submitted.

11.6 Recommendations on Postmarketing Actions

No postmarketing studies are recommended.

APPENDIX 1. CRMTS #9311 APRIL 30, 2014, PRE-BLA MEETING MINUTES

Our Reference:	CRMTS # 9311 PS002352
TODAY'S DATE:	**April 30, 2014 PAGES:** 5
TO:	**Paul L. Roney, Ph.D., DABT** (b) (6) **Wioletta Nisiobedzka** Regulatory Affairs, Project Manager Bio Products Laboratory, Ltd. Phone number: (b) (6) Fax number: +44 (0)20 8957 2601 Email address: Wioletta.Nisiobedzka@bpl.co.uk
FROM:	**Raphael R. Rodriguez** Regulatory Project Manager Division of Blood Applications Office of Blood Research and Review Phone number: (b) (6) Fax number: 301-827-2857
SUBJECT:	Summary of FDA Internal Meeting [or Written Response to meeting request]
PRODUCT:	Albumin (Human), 5% and 25%

Although we continue to reserve May 8, 2014, for a teleconference with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us in writing as soon as possible so that we may clear the meeting time. These responses would then become the official FDA responses to your questions.
Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review team can provide clarification during the reserved meeting time. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our pre-meeting (preliminary) responses, we may not be prepared to discuss and/or to reach agreement on such changes at the meeting although we will try to do so if possible.
Please include a reference to CRMTS # 9311; PS002352, in your future submissions related to the subject product.

Questions from the Sponsor/Applicant:

Clinical Question:
Sponsor/Applicant Question 1:
BPL does not intend to provide additional clinical information and will base the product's indications on those shown to be effective in the literature.
Is this acceptable to FDA?

FDA Response to Question 1:
Clinical trials in adult subjects will not be required.
With respect to clinical trials in pediatric subjects,

a. Please submit an initial Pediatric Study Plan prior to initiation of any phase 3 studies. The initial Pediatric Study Plan should include an outline of the study you plan to conduct and any request for deferral or waiver, with supporting information (see paragraphs b and c, below). Enrolled subjects should range in age from 1 day – 12 years, with approximately equal numbers of subjects in the following subpopulations: 1 day – 2 yr, 2 yr – 6 yr, and 6 yr – 12 yr. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act.
b. Clinical trials in pediatric subjects age 0-12 can be deferred pending submission of a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies.
c. Clinical trials for efficacy in pediatric subjects 12-16 years, 11 months will be waived. Please note that extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies (i.e., safety cannot be extrapolated).

CMC Questions:
Sponsor/Applicant Question 2:
On the basis that a 25% product is the 'highest concentration product', BPL proposes to manufacture (b) (4) *conformance batches* (b) (4) *prior to BLA submission with a* (b) (4) *manufactured during the Pre-Approval Inspection (e.g. a total combination of* (b) (4) *batches and* (b) (4) *batch).*
Is this strategy acceptable to FDA?

FDA Response to Question 2:
No.
Data from a minimum of three consecutively manufactured conformance lots are needed in the BLA submission.
Sponsor/Applicant Question 3:
BPL intend to file with 6 months stability data on the conformance batches and provide concurrent stability updates during BLA review and post licensing. Extrapolation of stability seen under accelerated conditions will be compared to a statistical model for the data from the 4.5 and 20% products in line with Q1E Evaluation of Stability Data. Stability data on the 5% and 25% albumin (human) products is provided in Appendix 3.

Would FDA accept a shelf-life claim of 36 months at 2-25°C for 5% and 25% albumin based on this conformance batch data and supported by substantial stability data on UK-licensed 4.5% and 20% albumin?

FDA Response to Question 3:
Yes.
This is acceptable approach to file the submission. The final decision with regard to product's shelf-

life will be based on the review of the data submitted in the BLA.

Sponsor/Applicant Question 4:
The proposed specifications for 5% and 25% albumin (human) include tests specified in the (b) (4) *and 21CFR640.80 (see Tables 5 & 6 and Appendix 2) and also those deemed to be stability indicating.*
Would FDA accept (b) (4) *endotoxin only and permit the* (b) (4) *test to be dropped?*

FDA Response to Question 4:
Yes.
We agree that you may use (b) (4) in lieu of (b) (4) test.

Sponsor/Applicant Question 5:
Are there any other final product tests required to license these products in the USA?

FDA Response to Question 5:
Your approaches to identify the final product tests and specifications appeared to be acceptable. In general, the final product tests and specifications should include the requirements specified in CFR for Albumin (Human) products, and additional tests that are found in USP or European Pharmacopoeia for Albumin (Human) solutions.

Sponsor/Applicant Question 6:
The rationale stated by the FDA in 2000[2] for setting the limits to the (b) (4) *caprylate concentration was based upon the difficulty in predicting the effects of the increased* (b) (4) *caprylate. The extensive safety record of the 4.5% and 20% Zenalb products has indicated that formulation with* (b) (4) *caprylate at* (b) (4) *millimole per gram of protein has not led to an increase in adverse reactions of concern (as shown in the PSUR see Appendix I).*

Would FDA license the proposed 5 and 25% albumin products with (b) (4) *stabilizer* (b) (4) *caprylate) at a concentration of* (b) (4) *millimole per gram protein given the extensive safety data from the UK and other overseas markets?*

FDA Response to Question 6:
No.
The new product needs to conform to CFR specifications as the minimum requirements. As pointed out correctly, the CFR stated that (b) (4) millimole (b) (4) caprylate, or (b) (4) millimole (b) (4) acetyltryptophanate and (b) (4) millimole (b) (4) caprylate per gram of protein". Therefore, the new albumin products will not be licensed with (b) (4) stabilizer (b) (4) caprylate) at a concentration of (b) (4) millimole per gram protein at this time.

Sponsor/Applicant Question 7:
If FDA would not consider licensing the 5% and 25% Albumin (human) products with a higher concentration of caprylate (as per Q5), development of a new formulation for 5% and 25% Albumin (human) is proposed, with the addition of sodium chloride to ensure that the sodium specification of 130 to 160 mEq is met and the use of dual stabilisers to ensure adequate stability (see Table C: BPL dual stabilizer formulation). The specifications for 5% and 25% albumin shown in Section 10.6: Tables 5 & 6, would be adjusted accordingly.

The purification of the active ingredient would be unchanged, but the excipients would be slightly modified. Changing the stabilising excipients may affect the stability of the product, although these stabilisers are very well established for albumin products and are well known to provide satisfactory stability during pasteurisation and long term storage at 25°C (77°F). The expiry date will be set using storage at +2 to +25°C (36 to 77 °F) with 12 months initially set, and extensions to shelf life justified by stability results. Stability will be compared to the current Zenalb products using a statistical model in line with Q1E Evaluation of Stability Data for all temperature conditions (real time and accelerated).

Is this acceptable to FDA?

FDA Response to Question 7:
Yes.
This approach appears to be acceptable in establishing the stability of the new albumin products as part of BLA to be submitted. As indicated in the response to Question 2, the product stability will be reviewed and evaluated in the BLA including the real time stability data, stability study results under accelerated conditions, and a statistical analysis and extrapolation of the data in comparison with that from the current 4.5 and 20% products.

PharmTox Questions:
Sponsor/Applicant Question 8:
N-acetyl tryptophan is widely used in combination with caprylate (octanoate) for dual stabilized Human albumin products (Table C). The proposed concentration of N-acetyl tryptophan and caprylate in the reformulated 5%/25% albumin would be the same as for other well established albumin products, ie. both stabilizers at (b) (4) *. Table C above shows that currently marketed albumin products all contain the same stabilizers at the same concentration of* (b) (4) *mmol/g albumin. Stabilizer details for the current and proposed reformulated BPL albumin products are also given in the table.*

BPL does not anticipate submitting any new preclinical data for the new formulation if N-acetyl tryptophan is added as a second stabiliser, however a literature review on relevant toxicology data will be undertaken and presented in Module 2.

Is this acceptable to FDA

FDA Response to Question 8:
Yes. It is acceptable.
Concurrence Page
Reference Number: CRMTS #9311
PS002352
Letter Type: Preliminary Meeting Response
History: Drafted: Raphael Rodriguez/ April 30, 2014
Revised: Mark Shields/
Revised: Yiping Jia/ April 30, 2014
Revised: Jin Baek/
Revised: Laurence Landow/ April 30, 2014
Revised: Nisha Jain/

Revised: Paul D. Mintz/
Howard Chazin

APPENDIX 2. HYPOVOLEMIA FOLLOWING SHOCK DUE TO TRAUMA OR SEPSIS: SUMMARY OF KEY RCTS.

Trial	**N (albumin / comparator)**	**Setting**	**Study design**	**Endpoints**	**Posology**	**Main results**	**Safety results (adverse events)**
Finfer et al., 2004 (SAFE study)	6997 (3497/3500)	ICU (trauma, sepsis, ARDS) (SAFE study)	Comparative, multi-center, randomized, double-blind trial	Primary: death from any case during 28 days after randomisation		Deaths: n= 726 (albumin group) n= 729 (saline group) relative risk of death, 0.99; 95% CI: 0.91 - 1.09; p = 0.87	Adverse events not reported in publication
The SAFE study investigators (2011)	1218 (603/615)	ICU Severe sepsis (subgroup/ SAFE study)	Pre-defined subgroup analysis of SAFE study		Sub-analysis of SAFE study	Adjusted odds ratio for death for albumin *versus* saline was 0.71 (95 % CI: 0.52 - 0.97; p = 0.03).	Adverse events not reported in publication

Trial	**N (albumin / comparator)**	**Setting**	**Study design**	**Endpoints**	**Posology**	**Main results**	**Safety results (adverse events)**
Bellomo et al., 2006	691 (339/352)	See SAFE study	Nested cohort study within SAFE study		Sub-analysis of SAFE study	No major differences in patients‟ acid-base variables between 2 groups	Adverse events not reported in publication
Bellomo et al., 2009	687 (338/349)	See SAFE study	Cohort of 687 critically ill patients		Sub-study of SAFE	Albumin or larger fluid volumes prolonged APTT	Adverse events not reported in publication

Trial	**N (albumin / comparator)**	**Setting**	**Study design**	**Endpoints**	**Posology**	**Main results**	**Safety results (adverse events)**
Finfer et al., 2006	See SAFE study	See SAFE study	See SAFE study		Sub-analysis of SAFE study	OR for death for albumin compared with saline for patients with a baseline serum albumin concentration of 25 g/L or less and more than 25 g/L were 0.87 and 1.09 (ratio of ORs 0.80, 95 % CI: 0.63 - 1.02)	Adverse events not reported in publication

Trial	**N (albumin / comparator)**	**Setting**	**Study design**	**Endpoints**	**Posology**	**Main results**	**Safety results (adverse events)**
Myburgh et al., 2007	460 (231/229)	Traumatic brain injury	*Post-hoc* follow-up study of SAFE		See SAFE study	24 months mortality: albumin group 33.2 %, saline group 20.4 % (relative risk, 1.63; 95 % CI: 1.17 - 2.26; p = 0.003).	Adverse events not reported in publication
Cooper et al., 2006	42 (19/23)	Thermal injury	Multicentre, non-blinded, controlled, randomized by centre	Primary: MODS to day 14 secondary: 28-day- mortality and others	Ringer lactate vs HSA 5% plus Ringer lactate	No significant difference between groups in the lowest MODS from Day 0 to Day 14 (p = 0.73)	28-day-mortality: HSA + RL: 3/19 RL: 1/23 Overall incidence of adverse events: comparable between groups

Trial	**N (albumin / comparator)**	**Setting**	**Study design**	**Endpoints**	**Posology**	**Main results**	**Safety results (adverse events)**
Trof et al., 2010+ and Van der Heijden et al., 2009	48 Colloids (incl. albumin) vs saline+	ICU: sepsis vs nonsepsis	Single-centre, single-blinded, randomized study	Primary: fluid-loadinginduced increases in cardiac index	HSA 5% vs HES 6% vs gelatin 4 % vs saline	Increased cardiac index with colloids compared to saline solution, in both septic and nonseptic clinical hypovolemia	Adverse events not reported in publications
Dolecek et al., 2009	56 (30/26)	Severe sepsis and increased EVLW	Randomized controlled study	Main objective: Evolution of amount of EVLW Secondary: cardiorespiratory function, mortality	HSA 20% vs 6% HES (130/0.4)	Greater decrease of EVLW in HSA group than HES ($p < 0.05$)	Serious adverse events were recorded in the study, but not reported in publication Total mortality 18%, no differences between groups

Trial	**N (albumin / comparator)**	**Setting**	**Study design**	**Endpoints**	**Posology**	**Main results**	**Safety results (adverse events)**
Annane et al., 2013	2857 (n.a.)	Pts with sepsis, trauma, hypovolemic shock without sepsis or trauma; ICU	Multicenter, randomized study	Primary: death withi 28 days; secondary: 90.day mortality, days alive and without renal replacement therapy	Colloids vs crystalloids investigators could use whichever fluids were available at their ICU	28-day mortality: 25.4% (colloids) vs 27.0% (crystalloids) RR 0.96, 95% CI: 0.88 - 1.04; p = 0.26 90-day mortaliy:	Adverse events not reported in publication
Caironi et al., 2014	1818 (910 / 908)	Pts with severe sepsis; ICU	Multicenter, randomized, open- label, controlled study	Primary: death from any cause at 28 days	HSA 20% plus crystalloids vs. crystalloids alone	At 28 days after randomization, 31.8% of pts. in the albumin group and 32.0% in the crystalloid group had died (RR in the albumin group, 1.00; 95% CI: 0.87 - 1.14; p = 0.94)	Incidence of new organ failures during the study was similar in the 2 groups

Trial	**N (albumin / comparator)**	**Setting**	**Study design**	**Endpoints**	**Posology**	**Main results**	**Safety results (adverse events)**
Total number of patients included	Albumin: 4456 Comparator: 4457						

APPENDIX 3. TABLE 3 ALBUMIN USE IN CHILDREN WITH MALARIA: SUMMARY OF KEY RCTS

Trial	**N** (albumin / comparator)	**Setting**	**Study design**	**Endpoints**	**Posology**	**Main results**	**Safety results** (adverse events)
Akech et al., 2006	88 (44/44)	Children > 3 months with severe falciparium malaria, metabolic acidosis and shock	Quasi-randomized phase 2 study	Primary: resolution of acidosis and shock secondary: mortality, adverse events, neurological sequelae	HSA 4.5% vs Gelofusine 4%	Resolution of shock and metabolic acidosis were similar between groups	Mortality: 2.3% (HSA) 15.9% (Gelofusine)

Maitland et al., 2005a	61 (23/20/18)	Children > 2 months, with severe malarial anemia (Hb <5g/dL) with acidosis	Randomized, controlled	Primary: reduction in base access between admission and 8h	HSA 4.5% vs saline vs maintenance only	No significant difference in the mean percentage reduction in base excess between admission and 8 h (95% CI): HSA: 44% (32–57%), saline: 36% (16–57%); control: 42% (19–66%)	Mortality rate 16% (95% CI: 8-28%) no difference in mortality between groups

Maitland et al., 2005b	150 (56/61/33)	Children with severe malaria and acidosis (median age: 2.8 yrs)	Randomized, controlled, open label	Primary outcome measure: % reduction in base deficit at 8h	HSA 4.5% vs saline vs control group; 20 mL/kg (base deficit 8-15 mmol/L) or 40 mL/kg (base deficit >15 mmol/L)	No significant difference in the resolution of acidosis between the groups; mortality rate was significantly lower among patients who received HSA	Mortality, pulmonary edema, neurological deterioration: more common in saline recipients
Total number of patients included	**Albumin: 123 Comparator: 125**						

Appendix 4. **Table 4A and Table 4B**

TABLE 4A: HYPOVOLEMIA POST-SURGERY (CARDIAC / NON-CARDIAC): SUMMARY OF KEY RCTS IN ADULT PATIENTS

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse**
Magder and Lagonidis, 1999	28 (13/15)	Cardiac surgery (CPB/ ICU)	Randomized, non-blinded	Right arterial pressure, cardiac output	HSA 25% 100mL vs saline	HSA 25% seemed to have an inotropic effect	Adverse events are not reported in the publication
Vogt et al., 1999	50 (25/25)	Urological surgery	Single-centre	Hemodynamic, coagulation, renal function parameters	HSA 5% vs HES 6% (200/0.5); 4 peri-operative days	Hemodynamic, coagulation, renal function parameters showed no difference between the two groups	Adverse events are not reported in the publication HES group: moderate postoperative increase in APTT No intolerance reactions

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse**
Ernest et al., 2001	40 (23/17)	Cardiac surgery	Prospective, randomized, non-blinded	Hemodynamic parameters	HSA 5% vs saline	HSA 5% was approx. 5 times more efficient as plasma volume expander compared to saline	Adverse events are not reported in the publication
Arellano et al., 2005	50 (25/25)	Head and neck surgery	Prospective, randomized, triple-blinded study	Hemostatic effects/ coagulation variables	HSA 5% vs HES 264/0.45; 24 h	HES 264/ 0.45 impaired coagulation to a greater extent than HSA: APTT, INR significantly increased ($p < 0.05$), FVIII, vWF significantly reduced ($p < 0.05$)	3 pts with potentially serious adverse events (n=2 HES; n=1 HSA)

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse**
Arya et al., 2006	30 (15/15)	CABG	Prospective, randomized study	Hemodynamic parameters	RL vs HSA 5% for ANH	Hemodynamic parameters were better maintained by HSA 5% than by RL	Adverse events are not reported in the publication
Salinas et al., 2006	20 (10/10)	CABG	Prospective, randomized, double-blind study	Utility of the LVEDV measurement as a guide to cardiac index	HSA 5% or RL over 15 min	HSA infusion expanded plasma volume; both fluids temporarily increased LVEDV	Adverse events are not reported in the publication

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse**
Niemi et al., 2006	45 (15/30)	Cardiac surgery	Single-centre, randomized study	Blood coagulation assessed by thromboelastometry	HSA 4% vs HES 6% (200/0.5) vs gelatin 4%; no pre-set infusion times	HES and gelatin affected coagulation, albumin had no detrimental effect	Adverse events are not reported in the publication
Kuitenen et al., 2007	45 (15/30)	Cardiac surgery	Prospective, randomized, open-label study	Hemodynamic parameters (HR, MAP, CVP, CI, PCWP)	HSA 4% vs HES 6% vs gelatin 4%; 15 mL/kg bw; length of time of study not pre-set	In early postoperative phase after cardiac surgery, HSA and HES improved hemodynamics more and longer than gelatin	Adverse events were not observed

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse**
Niemi et al., 2008	45 (15/30)	Cardiac surgery	Prospective, open label, randomized	Hemodynamic parameters (HR, MAP, CVP, PCWP)	HSA 4% vs 6% HES (200/0.5) or (130/0.4) to keep CWP > 10 mmHg	HR, MAP, CVP, PCWP showed no significant difference between the groups	Adverse events are not reported in the publication

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse**
Yuan et al., 2008	127 (64/63)	Gastrointestinal surgery	Prospective, randomized, open-label	Postoperative hypoalbuminemia, nutritional status, fluid balance, complications, hospital stay	HSA 20% (100 mL/day for 3 days) vs saline	Postoperative plasma albumin, total protein, and prealbumin levels were similar in the 2 groups; no significant differences in overall fluid administration and urine output	Incidence of postoperative complications in the 2 groups was similar: 23.4% for the albumin group; 12.7% for the saline group (p = 0.116). Adverse events are not reported in the publication

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse**
Hecht-Dolnik et al., 2009	156 (78/78)	Off-pump CABG	Randomized	Risk of postoperative bleeding	1L hetastarch vs 1L albumin intraoperative (no details)	Hetastrach increased postoperative transfusion requirement and volume of	Adverse events are not reported in the publication
Yang et al., 2011	90 (30/60)	Hepatectomy in hepatocellular carcinoma	Prospective, randomized	Hemodynamic, liver function, inflammatory response parameters	HSA 20% vs HES 6% vs RL; 5 days	Total bilirubin, ALT, and AST did not differ significantly between groups. C-reactive protein was significantly lower in the HES group compared with the other groups.	Adverse events are not reported in the publication

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse**
Skhirtladze et al., 2014	240 (80/160)	Cardiovascular surgery on CPB	Randomized, double-blind, single-centre	Primary outcome: external blood loss from chest drains over 24h	HSA 5% vs. HES 6% vs RL; up to 50 mL/kg perioperatively	Chest tube drainage over 24h (main outcome variable) was not different between groups	Adverse events are not reported in the publication
Shah et al., 2014	80 (40/40)	Living donor renal transplantation	Prospective, randomized, double-blind, controlled	Early graft function	HSA 20% plus saline vs saline alone	No difference in outcome	Adverse events are not reported in the publication
Abdallah et al., 2014	44 (22/22)	End-stage renal disease pts undergoing kidney transplantation	Prospective, randomized	Post-transplant renal function until day 5 after surgery	HSA 20% plus saline vs saline alone	HSA 20% (plus saline) provides no benefit compared to saline alone	Adverse events are not reported in the publication

	N (albumin vs comparators)	Setting	Study design	Endpoints	Regimen	Main findings	Safety results (adverse
Total number of	**Albumin: 470 Comparators: 620**						

TABLE 4B: HYPOVOLEMIA POST-SURGERY (CARDIAC / NON-CARDIAC): SUMMARY OF KEY RCTS IN PEDIATRIC PATIENTS

	N (albumin vs comparators)	Setting	Study design	Endpoints	Regimen	Main findings	Safety results (adverse events)
Haas et al., 2007	42 (14/28)	Surgery children of 3 - 15 kg bw	Prospective, randomized	Parameters of hemostasis	HSA 5%, HES 6 %, or gelatin 4 %; 15 mL/kg over 30 min	Effects of colloids on clot formation in small children are comparable to those described in adults; HES: coagulation time increased significantly, and clot formation time, α angle, clot firmness, and fibrinogen/fibrin polymerisation were significantly more impaired than for HSA 5% or gelatin	Adverse events are not reported in the publication
Hildebrandt et al., 2007	30 (15/15)	Craniofacial surgery infants aged < 12 months	Prospective, pilot study	Coagulation parameters, clinical endpoints	FFP vs HSA 5%	Similar extent of clotting and fibrinolytic activation, no differences in clinical endpoints	Adverse events are not reported in the publication

	N (albumin vs comparators)	Setting	Study design	Endpoints	Regimen	Main findings	Safety results (adverse events)
Kerner et al., 2008	30 (15/15)	Craniofacial surgery infants aged < 12 months	Prospective, pilot study		FFP vs HSA 5%	Volume replacement in pCFS can be safely performed with both applied protocols	Adverse events are not reported in the publication
Standl et al., 2008	82 (41/41)	Non-cardiac surgery children < 2 years	Prospective, controlled, randomized, open-label, multi-center pilot study	Hemodynamic variables, coagulation parameters	HSA 5% vs HES 130/0.4 for perioperative volume management	Both, HES and HSA, were effective for hemodynamic stabilization	Adverse events were recorded, but details are not reported in the publication No differences in safety profiles between treatment groups

	N (albumin vs comparators)	Setting	Study design	Endpoints	Regimen	Main findings	Safety results (adverse events)
Hanart et al., 2009	119 (59/60)	Cardiac surgery with CPB in pediatric pts (age: 5 - 46 mths)	Prospective, randomized	Perioperative blood loss, intraoperative fluid requirements	HSA 4% vs HES 6% up to 50 mL/kg (including CPB priming fluid)	Blood loss was not different between groups; more children in HSA group required allogenic blood transfusions	Adverse events are not reported in the publication
van der Linden et al., 2013	55 (26/29)	Cardiac surgery pediatric pts. (age 2 - 12 yrs)	Prospective, randomized, controlled, parallel-group, double-blind	Primary: total volume of colloid infusion for intraoperative volume replacement incl. priming	HSA 5% vs 6% HES 130/0.4; up to 50mL/kg bw	HES showed equivalence to HSA with regard to volume replacement therapy	Incidence of adverse events up to postoperative day 28 did not differ between the groups
Total number of patients	**Albumin: 170 Comparators: 188**						

Appendix 5. **Table 5 Tables 5A and 5B**

TABLE 5A: USE OF ALBUMIN SOLUTIONS AS PRIMING SOLUTIONS FOR CARDIOPULMONARY BYPASS IN ADULT PATIENTS

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse events)**
Tigchelaar et al., 1998	33 (12/21)	CABG	Prospective, randomized	Hemodynamics, COP	4% HSA vs 2.5% HES vs 3% gelatin in priming solution	HSA is a safe CPB priming solution additive	Adverse events are not reported in the publication
Palanzo et al., 1999a	80 (80/0)	Cardiac surgery	Randomized	Platelet count drop	Different amounts of albumin used in different oxygenators	As little as 0.0375 g/100mL prime was effective	Adverse events are not reported in the publication
Palanzo et al., 1999b	60 (20/40)	Cardiac surgery	Randomized	Platelet count drop	3 different types of oxygenators, one with albumin in priming solution	The albumin group had significantly lower platelet count drop than other 2 groups	Adverse events are not reported in the publication

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse events)**
Boks et al., 2001	60 (40/20)	Cardiac surgery	Randomized	Oxygenator resistance, platelet activation	20g albumin vs 2g albumin vs no albumin in 1600 mL colloidal prime	Albumin addition to CPB circuit that already contains colloids showed no effects	Adverse events are not reported in the publication
Kuitunen et al., 2004	45 (15/30)	CABG	Prospective, randomized	Hemostatic parameters	HES 120/0.7 vs HES 400/0.7 vs HSA 4% in the prime	Compared to HSA, HES solutions given with the CPB prime compromised hemostasis	n = 4 with new Q-wave in postoperative ECG; No strokes, no deaths

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse events)**
Rex et al., 2006	22 (11/11)	Cardiac surgery	Prospective, randomized, double-blind	Hemodynamics, volume status, cardiac function	HSA 4% vs RL as priming solution	HSA group: less fluid requirements and significantly reduced fluid shift to interstitium; no difference in short-term outcome (24 h)	Adverse events are not reported in the publication
Choi et al., 2010	36 (18/18)	Cardiac surgery; nonbiocompatible CPB circuit	Prospective, randomized, controlled	Primary: coagulation variables	HSA 5% vs 6% HES 130/0.4: 500mL added to priming solution of CPB circuit	HSA and HES had similar effects on coagulation variables, blood loss, pro-inflammatory activities	Adverse events are not reported in the publication

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse events)**
Kamra and Beney, 2012	20 (10/10)	Coronary bypass pts.	Prospective, randomized	Biopassivation	2.5g albumin in prime vs protein-free prime	Human albumin can passivate the synthetic surfaces of the extracorporeal circuit	Adverse events are not reported in the publication
Cho et al., 2014	54 (36/18)	Cardiac surgery	Randomized, controlled	Coagulation and inflammation parameters	HSA 5% vs 6% HES 130/0.4 in the prime	HES showed results comparable to the conventional fluid regimen with albumin	Adverse events are not reported in the publication
Total number of patients	**Albumin: 242 Comparators: 168**						

TABLE 5B: USE OF ALBUMIN SOLUTIONS AS PRIMING SOLUTIONS FOR CARDIOPULMONARY BYPASS IN PEDIATRIC PATIENTS

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse events)**
Riegger et al., 2002	86 (44/42)	Cardiac surgery pediatric (< 14 kg)	Prospective, randomized	Physiologic effects, clinical outcomes	HSA 5% vs crystalloid as prime	HSA in the prime may attenuate the extravasation of fluid out of the vascular space, but it may be associated with an increased transfusion rate	Complications and mortality were not significantly different between groups

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse events)**
Oliver et al., 2003	56 (28/28)	Cardiopulmonary bypass infants (< 10 kg bw)	Prospective, randomized, double-blind	Blood loss, transfusion requirements	FFP vs HSA 5% in the prime	Blood loss during first 24 h: similar between groups transfusions: HSA 5%: 6.1 ± 4.5 U FFP: 8.0 ± 4.2U (p = 0.035)	Adverse events are not reported in the publication
Loeffelbein et al., 2008	20 (10/10)	Cardiac surgery, neonates & infants	Randomized, blinded	Fluid balance, hemofiltration, capillary leakage, renal function	FFP vs FFP plus 20% HSA in the prime	Addition of HSA 20% reduced weight gain; no effect on renal	Adverse events are not reported in the publication
Yu et al., 2008	151 (151/0)	Cardiac surgery with CPB pediatric (age 2-36 months)	Prospective, randomized	Fluid parameters during 24 h	Prime with 3% vs 5% albumin	No significant clinical benefit from 5% vs 3%	Adverse events are not reported in the publication

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results (adverse events)**
Golab et al., 2011	70 (70/0)	Cardiac surgery pediatric (<10 kg bw)	Randomized	Fluid balance, body weight gain, clinical outcomes	Albumin in the prime to achieve standard COP or high COP	5% albumin in the prime and a COP target of 18mmHg during bypass showed potential benefit	Adverse events are not reported in the publication
Miao et al., 2014	60 (30/30)	Cardiac surgery with CPB pediatric (age 3months - 1.5 yr)	Prospective, randomized	Hemodynamic parameters, renal function during 6 h	6% HES 130/0.4 vs HSA 3.3% as CPB priming solution	Results for HES were equivalent to HSA	Adverse events are not reported in the publication
Total number of patients	**Albumin: 333 Comparators: 110**						

APPENDIX 6. **HYPOVOLEMIA IN BURN PATIENTS: SUMMARY OF KEY CLINICAL STUDIES**

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results** (adverse events)
Cooper et al., 2006	42 (19/23)	Thermal injury	Multi-centre, non-blinded, controlled, randomized by centre	Primary: MODS to day 14 - day-	Ringer lactate vs HSA 5% plus Ringer lactate	No significant difference between groups in the lowest MODS from Day 0 to Day 14 (p = 0.73)	28-day-mortality: HSA + RL: 3/19 RL: 1/23 Overall incidence of adverse events: comparable between groups
Cochran et al., 2007	202 (101/101)	Patients with ≥ 20 % TBSA burn injury	Case-control retrospective	Primary: mortality Secondary: time to resuscitation, ventilator days, length of hospital stay	Albumin vs no albumin	Mortality: HSA: 18.8% Control: 10.9% (OR 1.9, 95% CI: 0.8–4.2). Albumin was protective in a multivariate model of mortality (OR 0.27, 95% CI: 0.07–0.97)	Development of ARDS: HSA 65.3%, control: 37.6%; no differences in SIRS/sepsis

APPENDIX 7. **ALBUMIN IN THE TREATMENT OF PATIENTS WITH LIVER CIRRHOSIS AND ITS COMPLICATIONS: SUMMARY OF KEY CLINICAL TRIALS**

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Altman et al., 1998	60 (33/27)	Cirrhotic pts with ascites	Randomized, controlled, multi-center	Primary: renal failure or hyponatraemia within 15 days after paracentesis Secondary: tolerance of HES	HSA 20% (approx. 8 g/L of ascites removed) vs HES 6.5% (approx. 200 mL/L of ascites removed)	No difference in prevention of complications related to largevolume paracentesis	No pt. developed renal impairment; only 1 pt (HES) developed hyponatremia; HES was well tolerated except for hypoalbumine mia

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Sort et al., 1999	126 (63/63)	Pts with cirrhosis and spontaneous bacterial peritonitis	Randomized, multi-center	Development of renal impairment, mortality	Cefotaxime vs cefotaxime plus HSA (HSA 20%: 1.5 g/kg bw at diagnosis plus 1 g/kg bw on day 3)	HSA in addition to cefotaxime reduced the incidence of renal impairment (p = 0.002) and mortality during hospitalization (p = 0.01) in comparison with treatment with cefotaxime alone.	Mortality at 3 months: 41% vs 22% (p = 0.03)

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Brater et al., 2001	13	Cirrhotic pts with ascites	Randomized cross-over	Diuretic response, pharmacokinetics of furosemide	Albumin 25g IV alone vs furosemide 40mg IV alone vs albumin 25g + furosemide 40mg premixed *ex vivo* vs albumin 25g + furosemide 40mg simultaneously IV	Albumin did not enhance diuretic effect of furosemide; albumin did not alter the pharmacokinetics of furosemide	Adverse events are not reported in the publication
Zaak et al. 2001	35 (21/14)	Cirrhotic pts with ascites	Prospective	Efficacy, safety	Total paracentesis with albumin (5-8g/L ascites) vs reinfusion of ascites-ultrafiltrate		

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Garcia-Compean et al., 2002	69 with 96 LVP (48/48)	Pts with cirrhosis and tense ascites, total paracentesis	Randomized, controlled	Clinical, biochemical, hemodynamic, hormonal evaluations	HSA 20% vs low-molecular weight dextran 40 infused for 1 or 2 h; 8 g/L ascites removed	Dextran 40 was not as efficacious as albumin in preventing PICD ($p < 0.05$)	Complications: Dextran 40: 16% of pts, HSA: 22% of pts (n.s); Renal impairment: Dextran 40: 4% HSA 14% (n.s.); Deaths: Dextran 40: n = 18 HSA: n = 11 (n.s.)

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Gines et al., 2002	70 (35/35)	Pts with cirrhosis and refractory ascites	Randomized multi-center	Primary: survival without liver transplantation Secondary: complications of cirrhosis, costs	TIPS vs paracentesis plus IV albumin (8 g/L ascites removed)	Probability of survival without liver transplantation at 1 and 2 years: TIPS: 41% / 26% paracentesis: 35% / 30% (p = 0.51)	Adverse events are not reported in the publication

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Moreau et al. 2002	20 (10/10)	Pts with cirrhosis and tense ascites, paracentesis	Randomized, multi-center pilot study	Primary: changes in effective arterial blood volume Secondary: changes in serum creatinine, serum sodium, no. of pts developing renal impairment or hyponatremia	3 mg terlipressin vs HSA 20% (8 g/L of removed ascites; 50% within 2 hr, 50% 6 hr after paracentesis)	PRA: changes from baseline did not differ between groups (p = 0.39). 3 pts in each group developed decreased arterial blood volume. Changes in serum creatinine did not differ between groups	No pt developed renal impairment At 3 months, survival rate did not differ between groups

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Gentillini et al., 1999 Laffi et al., 2003	Protocol 1: 126 (63/63) Protocol 2 outpatient basis: 43/38	Cirrhotic pts with ascites receiving diuretics	Randomized, controlled	Protocol 1: disappearance of ascites, duration of hospital stay Protocol 2: reoccurrence of ascites, hospital readmission, survival	Diuretics vs diuretics plus HSA	Pts receiving diuretics plus HSA had a higher cumulative rate of response ($p < 0.05$) and a shorter hospital stay (20 ± 1 *versus* 24 ± 2 days, $p < 0.05$) Recurrence of ascites: diuretics alone: 94% diuretics + HSA: 51% ($p < 0.001$)	No side effects of HSA were observed

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Sola-Vera et al., 2003	72 (37/35)	Pts with cirrhosis and tense ascites, total paracentesis	Randomized, multi-center	Incidence of PICD	HSA 20% (8 g/L of ascites removed) vs saline 3.5 % (170 mL/ L ascites removed)	> 6 L of ascitic fluid removed: incidence of PICD was significantly higher in the saline group *versus* the albumin group (33.3% vs 11.4%, p = 0.03).	Complications other than PICD: Saline: 25.7% of pts HSA: 16.2% of pts

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Degoricija et al. 2003	50 (10/40)	Pts with cirrhosis and tense ascites	Randomized	Comparison of efficacy of 5 different treatment regimen	Paracentesis with 200 mL HSA 20% vs 600 mL FFP vs 900 mL gelatin vs paracentesis without volume expansion vs 40 mg furosemide iv	Albumin was superior to other plasma expanders in all aspects except cost	Adverse events are not reported in the publication
Fernandez et al., 2004	12 (12/0)	Pts with cirrhosis and spontaneous bacterial peritonitis	Open-label pilot study	Hemodynamics, renal function	Ceftriaxone plus HSA 20%	Albumin prevented deterioration of systemic hemodynamics and renal function	Adverse events are not reported in the publication

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Choi et al., 2005	42 (42/0)	Pts with cirrhosis and spontaneous bacterial peritonitis	Prospective, randomized, controlled	Survival rate at 6 and 12 months	LVP + albumin vs diuretics + albumin	No difference in efficacy, no difference in mortality	Long-term cumulative survivals were similar between groups
Fernandez et al., 2005	20 (10/10)	Pts with cirrhosis and spontaneous bacterial peritonitis treated with ceftriaxone	Randomized non-blinded pilot study	Improvement in systemic hemodynamics	HSA vs HES 200/0.5; 1.5 g/kg bw after baseline measurements, 1 g/kg bw on day 3	HSA but not HES reduced PRA and improved systemic hemodynamics	Adverse events are not reported in the publication

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Angeli et al., 2006	116 (116/0)	Pts with cirrhosis and spontaneous bacterial peritonitis	Multi-center, randomized, controlled	Efficacy of 2 antibiotic treatment regimen; effect of terlipressin plus albumin on type-1 HRS mortality	Ciprofloxacin switch therapy vs ceftazidime IV; terlipressin 2-12 mg/day + albumin 20-40g/day to maintain CVP at 12-14cm H2O	63% of type-1 HRS patients showed complete response, 11% showed partial, 26% showed no response	32% of type-1 HRS patients died during hospitalization; one patient underwent liver transplantation
Romanelli et al., 2006	100 (54/46)	Pts with first-onset cirrhosis	Randomized, non-blinded	Primary: survival without liver transplantation secondary: recurrence of ascites, other complications	Diuretics + HSA (1g/week in first year, 1g/2weeks thereafter) vs diuretics alone follow-up: 62.7 ± 4.2 months	Chronic albumin infusion resulted in a mean increase of survival of 16 months	No side effects caused by albumin administration were observed during whole study period

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Singh et al., 2006a	43 (22/21)	Pts with cirrhosis and tense ascites; paracentesis	Prospective randomized pilot study	Primary: development of PICD, defined as an increase in PRA of > 50% of pre-treatment value	3 mg terlipressin vs HSA, 8 g/L of ascites fluid removed	PRA and plasma aldosterone conc. before and 4-6 d after paracentesis were similar in both groups; both terlipressin and HSA prevented PICD.	Adverse events are not reported in the publication During hospital stay, no pts developed treatment-related complications

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Singh et al., 2006b	40 (20/20)	Pts with cirrhosis and tense ascites; paracentesis	Prospective randomized, controlled pilot study	Primary: development of PICD, defined as an increase in PRA of > 50 % of pre-treatment value	Noradrenaline, titrated by MAP vs HSA 8g/L of ascites fluid removed	PRA and plasma aldosterone conc. before and 6 d after paracentesis were similar in both groups. Noradrenaline was as effective as HSA in preventing PICD	Adverse events are not reported in the publication During hospital stay, no pts developed treatment-related complications

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Moreau et al., 2006	68 (30/38)	Pts with cirrhosis; paracentesis	Randomized, double blind controlled multi-center pilot study	Primary: occurrence of first liver-related complication	HSA 20% vs polygeline 3.5%	3.5% Time to first complication: did not differ between groups (p = 0.086) No. of liver-related complications: significantly lower with HSA (95% CI: -10.0 to -0.6; p = 0.018)	Only 1 serious AE reported (pulmonary edema with polygeline)
Lata et al., 2007	49 (25/24)	Pts with cirrhosis and tense ascites	Randomized multi-center	Hemodynamic, parameters	HSA 20% (8 g/L ascites removed) vs terlipressin	No statistically significant difference between groups in hemodynamic parameters	1 adverse event, not associated with study treatment

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Singh et al., 2008	40 (20/20)	Pts with cirrhosis and tense ascites	Prospective, randomized, controlled pilot study	Primary: development of PICD secondary: development of renal impairment or hyponatraemia	Midodrine po (dose to maintain MAP at 10 mmHg greater than baseline) vs albumin (8 g/L ascites removed)	PRA did not differ between groups 6 days after paracentesis; midodrine cheaper than albumin	2 pts/group developed treatment-related complications during hospital stay; follow-up: SBP in 1 albumin and 2 midodrine pts.
Appenrodt et al., 2008	24 (13/11)	Pts with cirrhosis and ascites	Randomized double-blind pilot study	Primary: development of PICD, defined as an increase of PRA of > 50% of pre-treatment value	Midodrine (12.5 mg three times per day; over 2 days) vs HSA (8 g/L of removed ascites)	PICD development: midodrine: n = 6 (60%) HSA: n = 4 (31%)	Adverse events are not reported in the publication 1 pt (midodrine) developed HRS type-1 on day 2

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Umgelter et al., 2008a	19 (19/0)	Cirrhotic ICU pts with tense ascites and acute renal failure (HRS)	Prospective uncontrolled	Circulatory parameters, renal function	HSA 20% up to 8g /L ascites removed; fluid therapy guided by hemodynamic parameters	Central blood volume was maintained by 20% HSA and improved renal function	1 death (pneumonia/ septic shock)

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Umgelter et al., 2008b	50 (50/0)	Pts with advanced cirrhosis	Prospective uncontrolled	To investigate the hemodynamic response to volume loading with hyperoncotic HSA, and to compare CVP and volumetric measures as markers of preload, and predictors of fluid responsiveness	2 x 200 mL HSA 20%	After HSA infusion, GEDVI, CI and CVP increased ($p < 0.001$; $p < 0.001$; $p < 0.001$ resp.), systemic vascular resistance decreased ($p < 0.001$)	Adverse events are not reported in the publication
Munoz et al., 2009	13 (13/0)	Pts with cirrhosis and type-1 HRS	Prospective open-label pilot study	Reversion of type-1 HRS	30-80g albumin/day plus terlipressin	HRS reversal in 61% of patients	Adverse events of terlipressin reported

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Alessandria et al., 2011	` 70 (70/0)	Pts with cirrhosis and tense ascites	Prospective, randomized, unblinded pilot study	Incidence of PICD	HSA 20% 4 g/L vs 8 g/L ascites removed	14 % of pts. in the 4 g/L and 20 % in the 8 g/L group developed PICD; rates of survival and of recurrence of ascites were not different between groups after 6 months	Number of complications other than PICD were similar between the 2 groups

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Boyer et al., 2011a	99 (subgroup)	Pts with acute or chronic liver disease and type-1 HRS; subgroup: transplant and non-transplant pts	Prospective, randomized, double-blind, placebocontrolled multi-center; subgroup analysis	Transplant-free survival, overall survival	Terlipressin + albumin vs albumin alone	Use of terlipressin plus albumin has no significant impact on posttransplant survival	Adverse events are not reported in the publication
Boyer et al., 2011b	112 (112/0)	Pts with acute or chronic liver disease and type-1 HRS	Prospective, randomized, double-blind, placebocontrolled multi-center; subgroup analysis	Predictive factors for response to terlipressin	Terlipressin + albumin vs albumin alone	Baseline creatinine is most consistent predictor of response to terlipressin	Adverse events are not reported in the publication

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Narahara et al., 2011	60 (30/30)	Pts with cirrhosis and refractory ascites	Randomized, controlled	Primary: survival Secondary: response to treatment, hepatic encephalopathy	TIPS vs paracentesis plus albumin (6 g/L ascites removed)	Cumulative probabilities of survival at 1 and 2 years: TIPS: 80 and 64% paracentesis: 49 and 35% ($p < 0.005$)	Treatment failure was more frequent in the paracentesis group, frequency of hepatic encephalopathy was greater in the TIPS group
Salerno et al., 2011	253 (99/0)	Pts with cirrhosis and renal failure, daily clinical practice	Prospective, observational cohort study	Prevalence of HRS, diagnostic criteria, treatment, 3 month outcome	Pts with HRS type-1: vasoconstrictor plus 27 ± 2 g albumin/day	HRS type-1: complete response in 30%, partial response in 20% 3 months survival: 19.7%	Adverse events are not reported in the publication

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Bari et al., 2012	25 (13/12)	Pts with cirrhosis and refractory ascites	Multi-center, randomized, double-blind, placebo - controlled pilot study	Recurrence of ascites, development of PCD	Octreotide im + midodrine po vs albumin (8g/L ascites removed)	Median time to recurrence of ascites: 10 days (HSA) vs 8 days (vasocontrictors), p = 0.318; no significant difference in PCD	Total adverse events: n = 4 in 3 pts (HSA) n= 5 in 4 pts (vasoconstrictors)
Guevara at al., 2012	110 (56/54)	Pts with cirrhosis and infections other than SBP	Randomized	Survival at 3 months	Antibiotics + albumin vs antibiotics alone	Treatment with albumin + antibiotics improved renal and circulatory functions and showed a potential survival benefit	At 3 months, 18 patients had died (10 in the control group and 8 in the albumin group) and 8 had been transplanted (2 and 6, respectively).

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Narahara et al., 2012	8 (8/0)	Cirrhotic patients with type-1 HRS	Prospective, multi-center, open-label, explorative study	Parameters of renal function	Terlipressin plus albumin (25.7 ± 2.8 g/day); follow up for 12 weeks	Treatment with terlipression plus albumin improved renal function; median survival time: 35 days	7 pts died during 12 week follow-up (4 liver failure; 1 HRS; 1 pneumonia; 1 CHF; 1 unknown cuase)
Hamdy et al., 2014	50 (25/25)	Pts with cirrhosis and tense refractory ascites	Prospective, randomized pilot study	Primary: development of PICD secondary: development of renal impairment, hyponatremia	Midodrine vs albumin (8 g/L ascites removed)	Midodrine is not as effective as albumin in preventing circulatory dysfunction after LVP	Midrodrine group: 7 pts died albumin group: no deaths, HRS or hepatic encephalopathy
Garcia-Martinez et al., 2015	12 + 10 (22/0)	Pts with refractory ascites; pts with acute decompensation of cirrhosis and AKI	Retrospective	Cardiac and renal hemodynamics; endothelial activation/dysfunction	Albumin 40-60 g/day for 3-4 days	Improvement of renal blood flow correlated with improvement in endothelial activation	No significant major adverse effects were observed

	N (albumin/ comparator)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main Findings**	**Safety results** (adverse events)
Total number of patients	**Albumin : 1313 comparator or placebo: 646**						

APPENDIX 8. **ALBUMIN IN NEPHROTIC SYNDROME: SUMMARY OF KEY CLINICAL STUDIES**

	N	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results** (adverse events)
Fliser et al. 1999	9	Pts with nephrotic syndrome	Randomized, double-blind, placebocontrolled cross-over	Primary: differences of mean urinary sodium and volume excretion in first 8 h after start of infusions	Furosemide 60 mg vs 200 mL HSA 20% vs combination	Coadministration of HSA increased response to furosemide by 20%	No side effects were observed
Na et al., 2001	7	Pts with nephrotic syndrome	Randomized, cross-over	Pharmacokinetics of furosemide; urine volume, sodium, chloride excretion	Furosemide 160mg vs 100mL HSA 20% + furosemide 160mg	Urine volume increased after pre-infusion of albumin; no changes in furosemide pharmacokinetic parameters	Adverse events are not reported in the publication
Dharmaraj et al., 2009	16	Children with nephrotic syndrome	Randomized, single-centre non-blinded cross-over	Primary: change in urine output and urine sodium excretion	Furosemide vs furosemide plus HSA 20% 1g/kg bw over 4 h	Urine volume: HSA + furosemide: 3.27 mL/kg h furosemide: 1.33 mL/kg h (p = 0.01)	2 pts exluded (metabolic acidosis; peritonitis) 3 pts withdrawn (edemafree;

	N	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results** (adverse events)
						Daily Na excretion: HSA + furosemide: 58 mEq Furosemide: 30 mEq (p = 0.08)	hypokalaemia
Ghafari et al. 2011	10	Pts with nephrotic syndrome	Randomized, cross-over	Urine volume, 24 h sodium excretion	Furosemide alone vs HSA alone vs combination	Co-administration of albumin and furosemide increased urine volume and Na excretion	Adverse events are not reported in the publication

APPENDIX 9. **ALBUMIN IN ACUTE RESPIRATORY DISTRESS SYNDROME: SUMMARY OF KEY CLINICAL STUDIES**

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results** (adverse events)
Martin et al., 2002	2002 37 (19/18)	ICU: pts with ALI and serum total protein ≤ 5.0 g/dL	Prospective, randomized, doubleblind, placebocontrolled study	Various clinical parameters	25g HSA every 8 h + furosemide for 5 days vs dual placebo		
Martin et al., 2005	40 (20/20)	ICU: acute lung injury/ARDS	Multi-center, randomized, doubleblind, placebocontrolled study	Primary: change in oxygenation over 24 hours	furosemide + HSA 25% vs furosemide + placebo	HSA-treated patients had greater increases in oxygenation (mean change in PaO2/FIO2: +43 vs -24 mmHg at 24 h and +49 vs -13 mmHg at day 3)	More frequent hypotension in the control group; no AEs (bleeding diatheses, transfusion requirements, or infectious complications) during the study

	N (albumin vs comparators)	**Setting**	**Study design**	**Endpoints**	**Regimen**	**Main findings**	**Safety results** (adverse events)
Kuper et al., 2007	13 15	ICU: pts with severe sepsis and ARDS	2 case series	Oxygenation and hemodynamic parameters after 4 h	1. 200 mL HSA 20% 2. 200 mL HSA 20% plus 30mg furosemide IV	No sustained improvement in oxygenation	Adverse events not reported