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Phase I Comparability of Recombinant Human Albumin and Human Serum Albumin

Dietrich Bosse, MD, Michaela Praus, MSc, Peter Kiessling, PhD, Lars Nyman, MD, Corina Andresen, MD, Joanne Waters, MSc, and Fritz Schindel, MSc

Recombinant human albumin (rHA) is a highly purified animal-, virus-, and prion-free product developed as an alternative to human serum albumin (HSA), to which it is structurally equivalent. The present investigation compared the safety, tolerability, and pharmacokinetics/pharmacodynamics of rHA with HSA. Two double-blind, randomized trials were performed in healthy volunteers using intramuscular (IM) and intravenous (IV) administration. The IM trial included 500 volunteers, each receiving 5 repeat doses of 5 mg (100 subjects), 15 mg (100 subjects), or 65 mg (300 subjects) of rHA or HSA. Thirty volunteers participated in the IV trial, each receiving ascending doses (10 g, 20 g, and 50 g) of either rHA or HSA. In both trials, all adverse events were recorded and conventionally classified; potential allergic responses were also monitored. Blood samples were taken in both studies to test for IgG or IgE antibodies against test products and potential impurities. For the IV study, pharmacokinetic/pharmacodynamic assessments were per-

formed, including measurement of serum albumin, colloid osmotic pressure, and hematocrit pre- and postinfusion. Nine subjects in the IM study (4 recipients of rHA and 5 of HSA) reported drug-related, potentially allergic events; all but 2 of these were skin related. No serious or potentially allergic events were reported with either product in the IV study. There was no immunological response to either product, and dose level did not influence the study outcomes. Serum albumin, colloid osmotic pressure changes, and hematocrit ratio were as expected, with no differences between rHA and HSA. rHA and HSA exhibited similar safety, tolerability, and pharmacokinetic/pharmacodynamic profiles, with no evidence of any immunological response.

Keywords: Recombinant human albumin; human serum albumin; drug safety; pharmacokinetics; pharmacodynamics

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Human serum albumin (HSA) is the most abundant protein found in plasma¹ and is a well-established product that has been used in clinical practice for many years. Its primary function as a therapeutic agent is restoration and maintenance of blood volume in situations such as traumatic shock, surgery and blood loss, treatment of burns, and plasma exchange.²⁻⁴ The properties of HSA, particularly lack of toxicity and immunogenicity, also make it an attractive candidate for use as a manufacturing component for other pharmaceutical and biological products—for example, as a stabilizer in vaccines and therapeutic protein drugs, in

coatings for medical devices, and as a component in drug delivery systems and imaging (eg, X-ray) reagents.^{1,5,6}

HSA is commonly produced by fractionation of plasma obtained from donors and is currently used in greater volumes than any other biopharmaceutical solution, with worldwide manufacturing on the order of hundreds of tonnes annually.⁴ The safety profile of HSA with respect to viral transmission has been excellent over the past 50 years.⁷ Nevertheless, the theoretical potential for the transmission of new and reemerging infectious agents (eg, hepatitis, human immunodeficiency virus, West Nile virus, variant Creutzfeldt-Jacob disease) with blood- and plasma-derived products is unlikely to be eliminated,^{2,8-11} and development of substitutes is recommended by regulatory authorities.¹² In view of increasing viral safety demands in the past 10 years, recombinant human albumin (rHA) has become an interesting and appropriate alternative to the use of HSA, especially for use as a

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component in widespread medications (eg, childhood vaccines). As well as the absence of pathogenic blood-derived infectious agents,^{8,9} the likely advantages of using rHA over HSA include increased batch-to-batch consistency.¹³

The investigated recombinant human albumin is a highly purified 20% rHA, which is structurally equivalent to HSA. It has been produced using a yeast expression system (*Saccharomyces cerevisiae*) further developed from that described by Goodey,³ without any human- or animal-derived materials and is therefore considered free of viruses or other infectious agents. Considering the intended uses of rHA as a replacement for animal- or human-derived agents such as gelatins or HSA, extensive studies have been performed to evaluate rHA's structure, function, and biochemical properties in direct comparison to the well-established HSA product.² Moreover, the recombinant human albumin was already successfully studied as culture media for oocytes of 85 women undergoing in vitro fertilization and may replace HSA in this setting to reduce the risk of prion contamination and transmission of plasma-derived impurities.¹⁴

The recombinant human albumin was developed specifically for use as an ingredient in pharmaceutical products—in the majority of cases, to replace the human-derived serum albumin.^{13,15} Many of the potential applications may involve repeated intramuscular, intravenous, or subcutaneous administrations.⁵ A clinical program was therefore developed to investigate the safety of this rHA using HSA as a direct comparator, following both intramuscular (IM) and intravenous (IV) administration. Central to the program was investigation of the potential antigenicity of the rHA product and its possible impurities (eg, host cell proteins and mannosylated rHA) versus HSA under what was considered a worse-case scenario. The product's pharmacokinetic/pharmacodynamic properties were also characterized and compared with HSA.

METHODS

The study was carried out in accordance with the International Conference on Harmonization (ICH) good clinical practice guidelines.

Study Participants

The participants were selected from a pool of healthy male and female volunteers in Uppsala, Sweden. Volunteers were eligible for inclusion in the study, provided that they were 18 years of age or older, had a body mass index of 19 to 29, and were willing to comply

with the study requirements. In addition, female subjects took adequate precautions against pregnancy.

Exclusion criteria were pregnancy; indication of active hepatitis; history of chronic hepatic, renal, autoimmune, cardiac, or pulmonary disease; history of allergic reaction to *S. cerevisiae* or yeast products; or history of alcohol, narcotic, or drug abuse. Volunteers with a history of anaphylactic or severe systemic response to human plasma proteins or who had received systemic treatment with corticosteroids or human plasma derivatives during the month prior to the study were also excluded.

The IgE status of all subjects included in the trials was evaluated using commercially available radio-allergosorbent test (RAST) methods (Phadiatope, Pharmacia) to give an indication of the atopic status of the study population, particularly any hypersensitivity to yeast. Subjects were tested against a pool of common environmental allergens (eg, mite, horse, dog and cat epithelium, mold, mugwort, timothy, and birch) and tested specifically against the yeasts *S. cerevisiae* and *Candida albicans*. No subjects, including those RAST positive to yeast, were excluded from the study on the basis of their RAST results.

Study Design

Two double-blind, randomized, phase I trials (one using IM and one using IV administration) were performed, each with 3 dose levels of rHA (Recombunin 20%, Delta Biotechnology Ltd, Nottingham, UK) and HSA (Human-Albumin N 20%, Bayer, Germany).

The IM administration regime was designed to simulate chronic exposure to rHA if used as an excipient, as well as being similar to an aggressive accelerated vaccination schedule (eg, emergency rabies vaccination), in the potentially most immunogenic route. The IV study was designed with the aim of simulating conventional intravenous applications of HSA at therapeutic doses.

Five hundred volunteers were enrolled for the IM trial (which was conducted under a Food and Drug Administration investigational new drug process) and randomized (1:1) to receive either rHA or HSA. The study was performed in 3 separate phases for the investigation of the 3 dose levels: 5 mg (100 subjects), 15 mg (100 subjects), and 65 mg (100 subjects). An additional 200 subjects received the highest tolerated dose (65 mg). With an expected incidence of 5% potentially allergic events for the HSA treatment group, the power to detect a 3-fold increase of such events under rHA treatment was 80% for the 65-mg dose group and 95% for all doses combined.

Following each dosing step, safety data were reported to an independent data safety monitoring board for review, which then made a recommendation to proceed with the next higher dose level. Recipients at each dose level were injected 5 times at 1-week intervals (ie, on days 1, 8, 15, 22, and 29). Final assessments were performed 7 days after the final dose, and therefore the study duration was 36 days.

For the IV trial, a total of 30 healthy volunteers were enrolled and randomized (1:1) to receive either rHA or HSA. The duration of the study was 50 days, with each participant receiving 3 consecutive doses at 3-week intervals of 10 g on day 1, 20 g on day 22, and 50 g on day 43 (total 80 g). Following application of the 50-g dose on day 43, subjects were monitored for 24 hours, mainly for assessment of pharmacodynamic parameters over time following the infusion. Final assessments were performed 7 days after the final dose, on day 50.

With no prior data on colloid osmotic pressure (COP, the main pharmacodynamic endpoint), the sample size for the IV trial was chosen arbitrarily; a post hoc examination of COP results showed, however, that the conventional 2 standard error intervals for the mean COP values (± 2 SEM) following the highest applied dose were within 10% of the mean.

Measurement of the frequency and severity of adverse events (AEs) was performed from the time of the first administration of the study drug (baseline) until the subject underwent a final examination. An additional category, potentially allergic events, was used—this was predefined in the study protocol as symptoms of allergy during the study period (ie, reddening [erythema] at the injection site or other parts of the body, exanthemas, urticaria, dyspnea, symptomatic decrease in blood pressure [within 24 hours], arthritis, nephritis, or neurologic symptoms). Nausea, vomiting, and abdominal pain were also defined as potentially allergic events, if considered study drug related. As with all adverse events, a potentially allergic event could be classed as mild, moderate, or serious.

For each investigated dose in both trials, *P* values for between-group differences in potentially allergic events and serious adverse events were derived from a 1-sided Fisher test.

Blood samples were taken at baseline (prior to administration) and 1 week following the final administration in both trials to investigate for the presence of IgG or IgE antibodies raised against the test products (rHA and HSA) and potential impurities (mannosylated rHA and yeast-derived antigens). Additional blood samples were taken 1 week after each dose for antibody analysis in the event of potentially allergic

events. Measurement of IgG antibody was by antibody capture enzyme-linked immunosorbent assay (ELISA); IgE measurements were by antigen capture ELISA. The limits of quantitation (LOQ) for the IgG assays were established individually for each plate but ranged from 0.16 to 0.63 $\mu\text{g/mL}$. For all IgE assays, the LOQ was 0.56 $\mu\text{g/mL}$. For the pharmacodynamic assessments in the IV trial, measurements of COP and the hematocrit ratio were performed. COP was measured using an Osmomat 050 (Gentech, Berlin, Germany) device. The hematocrit ratio was calculated by the ratio of pre- and postinfusion values ($\text{Hct}_1/\text{Hct}_2$). In addition, albumin concentration in serum was measured by ELISA. Assessments were performed 5 minutes and 2 hours after infusion of study drugs on days 1 (baseline) and 22. In addition, 24-hour assessment was performed on days 43 to 44, and final measurements were performed 7 days after administration of the last dose (day 50).

RESULTS

Background Characteristics

The demographics of each study population are given in Table I, indicating a high degree of similarity in the characteristics both within and between treatment groups in the 2 trials. Subjects with positive RAST results to common allergens (Phadiatope test) and to *S. cerevisiae* or *C. albicans* were found in both rHA and HSA treatment groups at similar levels. There were no withdrawals from the IM trial. Two subjects withdrew from the IV trial before receiving the third dose, both from the HSA group (1 subject withdrew his consent, and 1 demonstrated noncompliance with the study protocol by exhibiting a positive urine test for benzodiazepine). Thus, the safety population comprised 500 and 30 subjects for the IM and IV trials, respectively. Of the IV subjects, pharmacodynamic measurements were available for 30 out of 30 subjects at baseline on day 22, as well as for 28 out of 30 subjects on days 43 to 44 and 50 due to the withdrawals described above.

Adverse Events

Within the IM trial, AEs were reported in 99 (39.6%) recipients of rHA compared with 106 (42.4%) in the HSA groups (Table II). All but 2 of these events were of mild or moderate intensity, and most were headache or rhinitis (Table III). AEs that were considered possibly related to study treatment by the investigators affected 6 recipients (2.4%) of both rHA and HSA. Potentially allergic events were reported in 15 subjects (8 rHA, 7 HSA); these were considered related to study treatment

Table I Baseline Demographics in the 2 Phase I Trials, by Treatment Group

	Treatment Group									
	5 mg (IM)		15 mg (IM)		65 mg (IM)		10-50 g (IV)			
	rHA (n = 50)	HSA (n = 50)	rHA (n = 50)	HSA (n = 50)	rHA (n = 150)	HSA (n = 150)	rHA (n = 15)	HSA (n = 15)	rHA (n = 15)	HSA (n = 15)
Median age (range)	23 (18-34)	24 (18-51)	24 (18-41)	24 (18-49)	23 (18-52)	24 (18-69)	24 (19-33)	23 (19-52)		
Gender, n (%)										
Male	29 (58)	31 (62)	31 (62)	29 (58)	73 (49)	69 (46)	8 (53)	8 (53)		
Female	21 (42)	19 (38)	19 (38)	21 (42)	77 (51)	81 (54)	7 (47)	7 (47)		
Median body mass index, kg/m ² (range)	22.4 (19.8-28.9)	23.0 (19.1-27.4)	23.3 (19.0-29.0)	23.8 (19.6-28.5)	22.6 (19.0-28.4)	22.2 (19.0-28.7)	22.7 (19.4-25.2)	22.6 (19.3-28.1)		
Positive RAST, n (%)										
Phadiatope	17 (34)	19 (38)	19 (38)	18 (36)	58 (39)	45 (30)	3 (20)	4 (27)		
<i>Saccharomyces cerevisiae</i>	1 (2)	2 (4)	—	1 (2)	7 (5)	4 (3)	1 (7)	—		
<i>Candida albicans</i>	2 (4)	2 (4)	2 (4)	2 (4)	12 (8)	5 (3)	1 (7)	—		

rHA, recombinant human albumin; HSA, human serum albumin; IM, intramuscular; IV, intravenous; RAST, radioallergosorbent test.

Table II Proportions of Subjects Reporting Adverse Events in the 2 Trials, by Treatment Group

	Treatment Group							
	5 mg (IM)		15 mg (IM)		65 mg (IM)		10-50 g (IV)	
	rHA (n = 50)	HSA (n = 50)	rHA (n = 50)	HSA (n = 50)	rHA (n = 150)	HSA (n = 150)	rHA (n = 15)	HSA (n = 15)
Adverse events (all)	19 (38)	23 (46)	22 (44)	19 (38)	58 (39)	64 (43)	6 (40)	8 (53)
Adverse events (treatment related)	2 (4)	1 (2)	1 (2)	3 (6)	3 (2)	2 (1)	1 (6.7)	—
Potentially allergic event (all)	2 (4)	1 (2)	1 (2)	3 (6)	5 (3)	3 (2)	—	—
Potentially allergic events (treatment related)	1 (2)	1 (2)	—	2 (4)	3 (2)	2 (1)	—	—

Values are n (%). rHA, recombinant human albumin; HSA, human serum albumin; IM, intramuscular; IV, intravenous.

in 9 cases (4 rHA, 5 HSA). All but 2 of these events were skin related (Table III). There were no significant between-group differences in the incidence of potentially allergic events for any given dose, and there was no apparent association between dose and the incidence of these events. One serious adverse event was reported in 1 recipient of the 65-mg dose of HSA. This consisted of a ruptured ovarian cyst and was deemed unrelated to study treatment.

Within the IV trial, AEs were reported by 6 (40%) subjects in the rHA group and 8 (53%) in the HSA group (Table II). These were mostly headache and rhinitis (Table III). All AEs were mild or moderate in severity, and only 1 (affecting a subject in the rHA group) was considered related to study treatment. No serious or potentially allergic events were reported in either study group. There was no apparent increase in AEs with increasing dose.

Antibody Analysis

There were no clinically relevant changes in IgG or IgE for any of the 4 antigens (HSA, rHA, mannosylated rHA, and yeast-derived proteins) during either trial. This finding applied to all of the treatment groups, including subjects reporting potential allergic events.

In both trials, IgG against the yeast production strain (>95% subjects) and mannosylated rHA (>50% of subjects) were observed at baseline for both the rHA and HSA recipients, but no relevant increases in these levels were detected after administration (Figures 1 and 2). These predose positive antibody concentrations are not unexpected and are due to cross-reactivity between the production strain antigen preparation and antibodies produced as part of the normal humoral response to

Table III Incidence of Specific Adverse Events and Treatment-Related Potentially Allergic Events in the 2 Trials

	Incidence			
	IM Study		IV Study	
	rHA (n = 250)	HSA (n = 250)	rHA (n = 15)	HSA (n = 15)
Adverse events (all) ^a				
Headache	23 (9.2)	33 (13.2)	2 (13)	4 (27)
Pharyngitis	3 (1.2)	5 (2)	—	—
Rhinitis	41 (16.4)	46 (18.4)	4 (27)	3 (20)
Dysmenorrhea	3 (1.2)	9 (3.6)	—	—
Treatment related ^b				
Reddening at injection site	—	2 (0.8)	—	—
Reddening/swelling at other sites	1 (0.4)	3 (1.2)	—	—
Exanthema	2 (0.8)	—	—	—
Nausea	1 (0.4)	—	—	—
Abdominal pain	—	1 (0.4)	—	—

Values are number of subjects affected (%). rHA, recombinant human albumin; HSA, human serum albumin; IM, intramuscular; IV, intravenous.

a. Events occurring in at least 2 subjects in the IV trial and in at least 5 subjects in the IM trial.

b. All treatment-related potentially allergic events are shown.

environmental yeasts (eg, species of *Candida* and *Saccharomyces*).^{16,17} In the case of the mannosylated rHA, the cross-reactivity would be due to antibodies produced to naturally occurring yeast glycoproteins and the mannose moiety on rHA that is introduced by

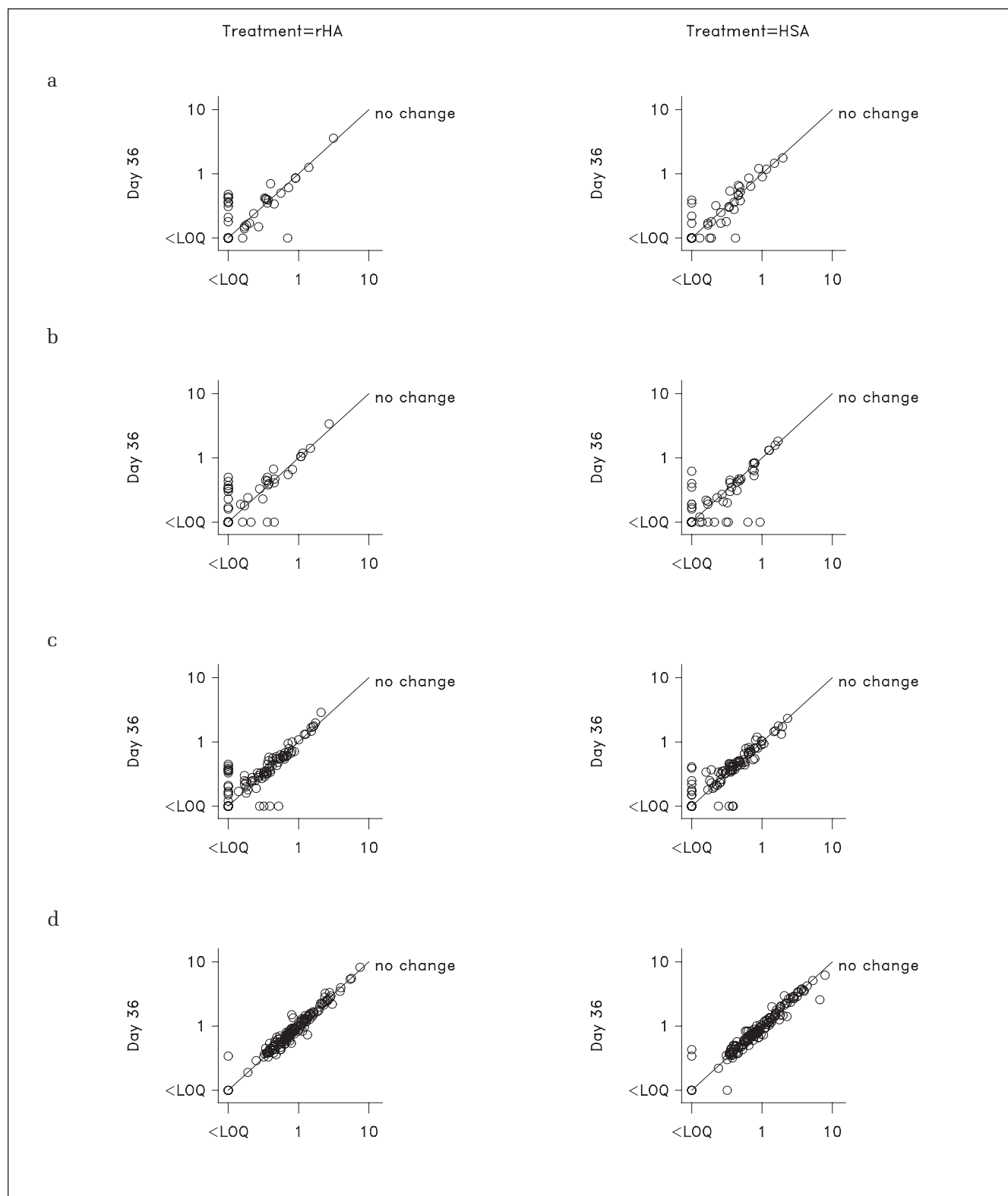


Figure 1. Shift graphs for IgG ($\mu\text{g/mL}$) against (a) recombinant human albumin (rHA), (b) human serum albumin (HSA), (c) mannosylated rHA, and (d) yeast for the intramuscular (IM) 65-mg treatment group (5-mg and 15-mg study group data, not shown, were comparable).

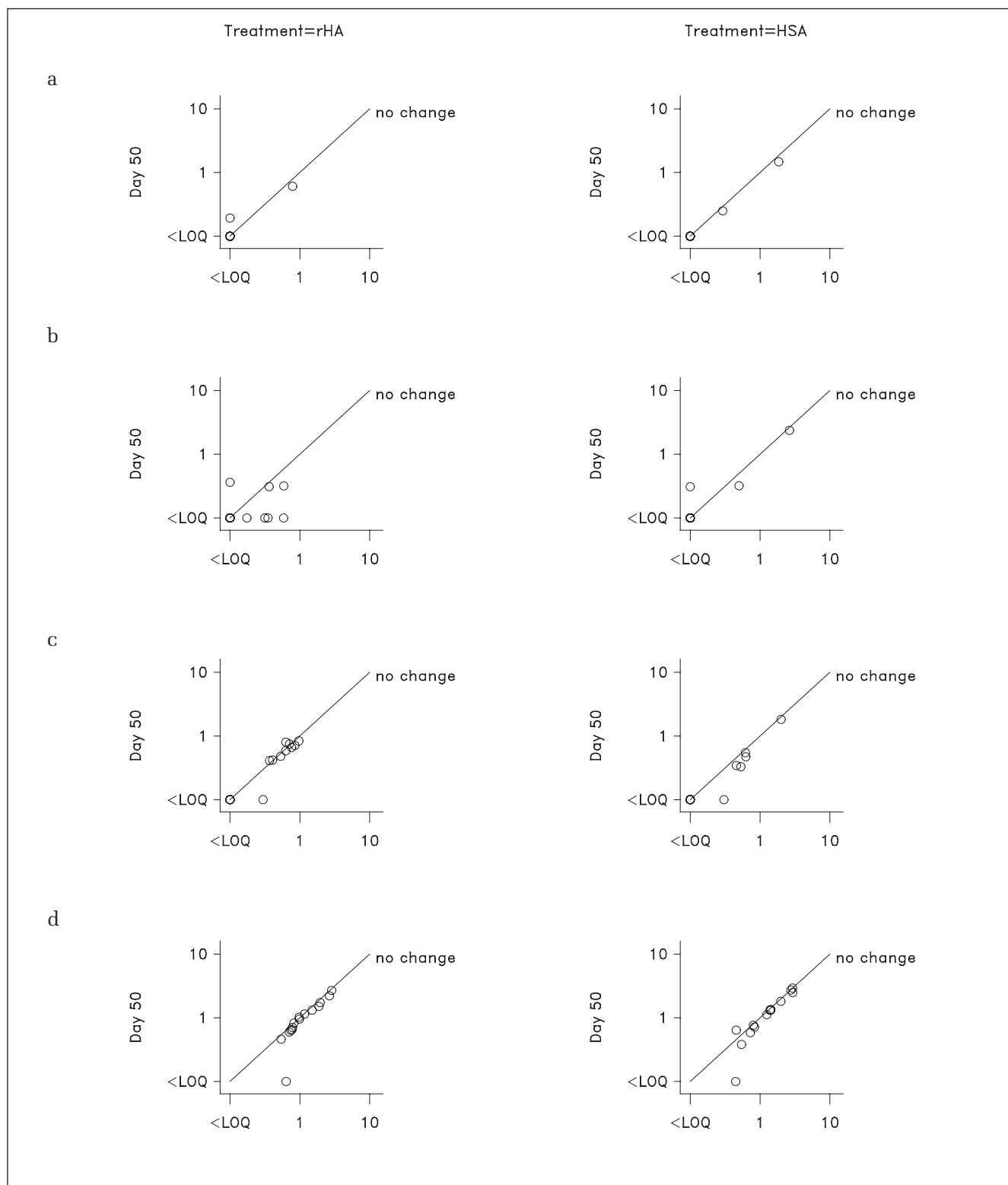


Figure 2. Shift graphs for IgG ($\mu\text{g/mL}$) against (a) recombinant human albumin (rHA), (b) human serum albumin (HSA), (c) mannosylated rHA, and (d) yeast for the intravenous (IV) treatment group.

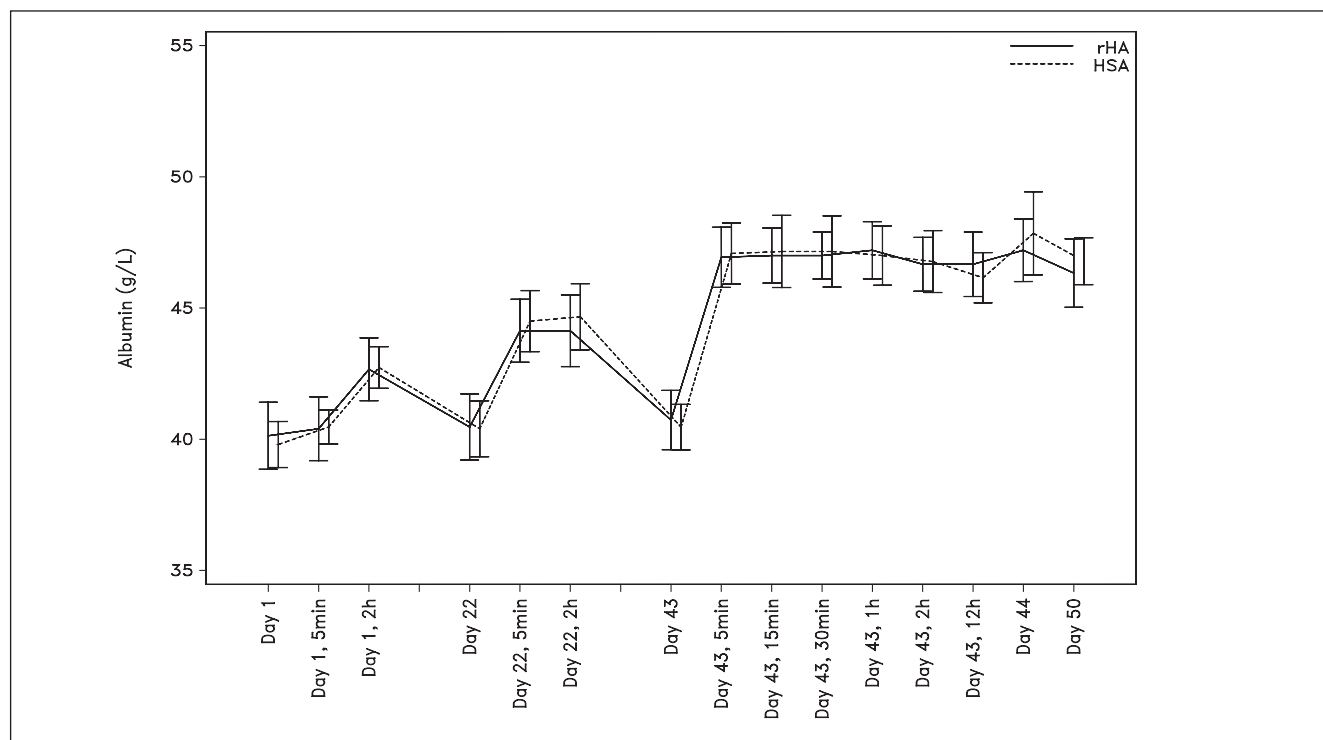


Figure 3. Mean (± 2 SEM) albumin concentrations (g/L) for the intravenous (IV) treatment group.

the yeast production strain.^{16,18} For the majority of subjects, the levels of rHA- and HSA-specific IgG were below the limit of quantification at baseline; again, there were no relevant increases after administration (Figures 1 and 2).

Only 4 subjects (3 rHA, 1 HSA; all from the IM trial) had detectable levels of IgE prior to treatment on day 1. In each case, the IgE specificity was for yeast protein (most likely due to exposure to naturally occurring yeast antigens in the environment). However, no significant postdose increase was observed in any of these subjects. None of the subjects showed detectable IgE to HSA, rHA, or mannosylated rHA on day 1 prior to treatment with rHA or HSA. After treatment, the follow-up investigation revealed only 1 subject with an increased IgE value against mannosylated rHA. This participant of the IM trial received HSA and did not experience any potentially allergic events. Shift graphs are not provided for the IgE analysis because almost all values were below the limit of quantification.

Pharmacokinetics and Pharmacodynamics

Serum albumin concentrations in the IV trial increased in both treatment groups (Figure 3), with highest values after the 50-g dose; rHA and HSA treatment showed a

very similar course of serum albumin concentrations, with increased values persisting until day 50.

The observed pharmacodynamic effects of rHA and HSA in the IV trial were in close agreement. Both rHA and HSA infusions were well tolerated at the administered doses of 10, 20, and 50 g. As expected, COP values increased moderately and remained highest 7 days after the third dose (day 50), which reflected the course of the albumin levels (Figure 4). The extent of hemodilution (hematocrit ratio) was moderate, even with the highest administered dose of 50 g (Figure 5). Hematocrit ratios reached peak mean values of 1.08 after the highest dose under either treatment.

The observed increase in albumin levels, combined with the maximum extent of hemodilution after the 50-g dose, suggested a moderate volume expansion. Distribution of the infused albumin beyond the central plasma compartment was likely because the observed increase of serum albumin concentrations after the 50-g dose (approximately 7 g/L) was clearly less than expected from distribution to plasma alone.

DISCUSSION

This is the first clinical program reporting the safety, tolerability, and pharmacokinetics/pharmacodynamics of rHA in healthy human volunteers. Overall, the ob-

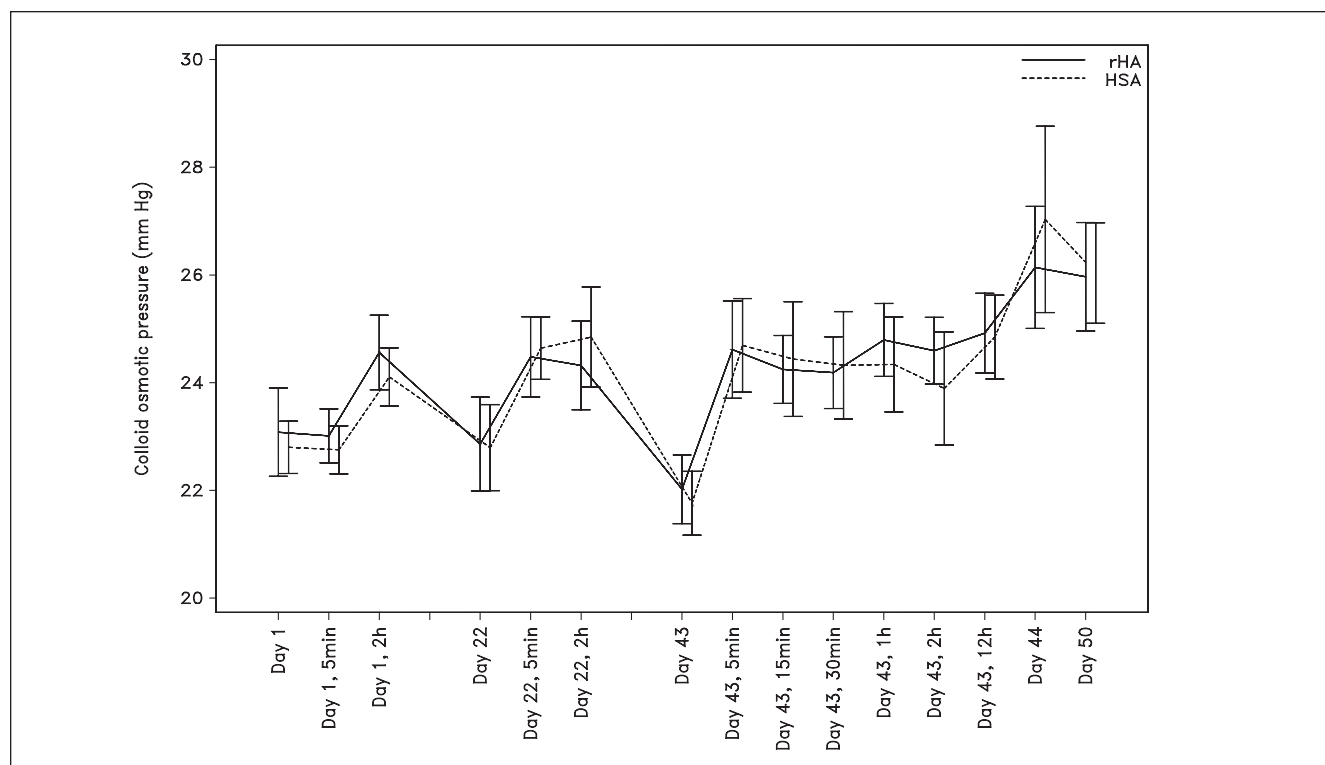


Figure 4. Mean (± 2 SEM) colloid osmotic pressure (mmHg) for the intravenous (IV) treatment group.

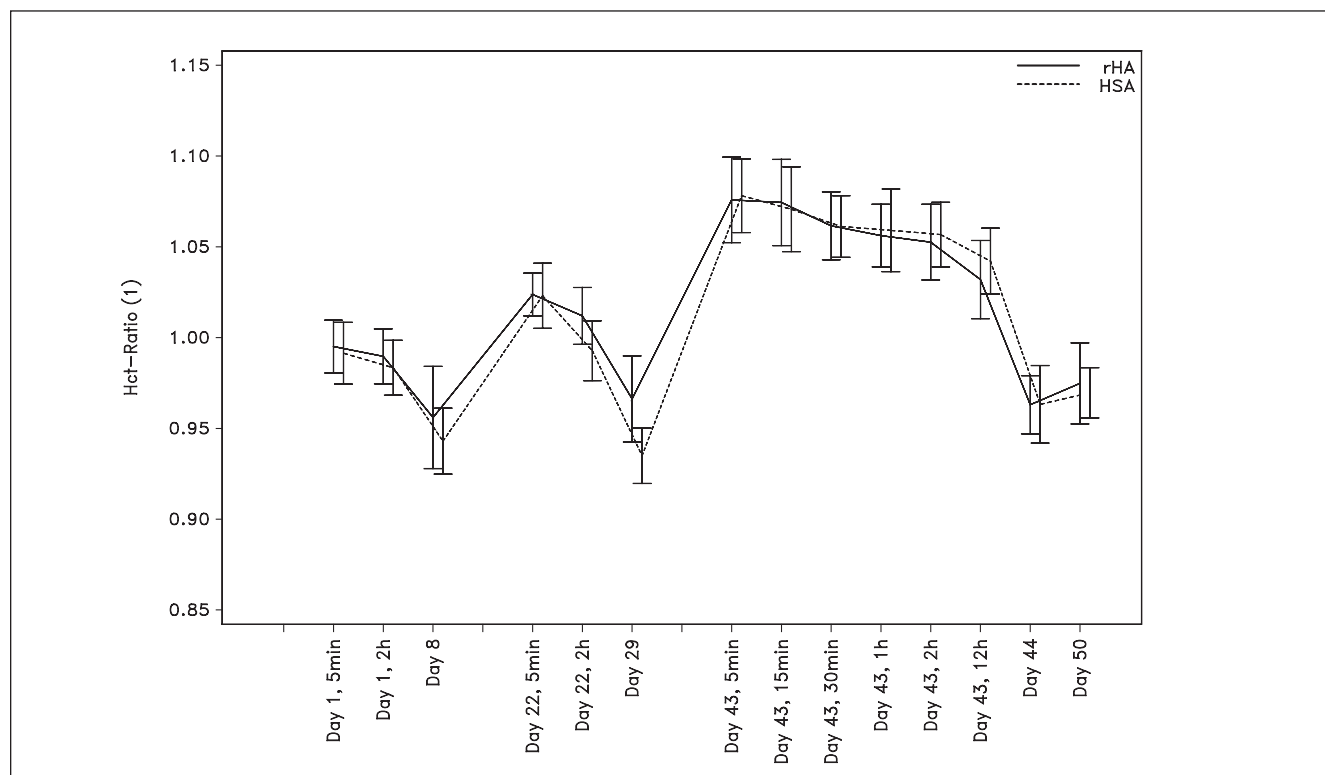


Figure 5. Mean (± 2 SEM) hematocrit ratio (1) for the intravenous (IV) treatment group. Hct, hematocrit.

served safety and pharmacodynamic profiles of rHA and HSA for all dose levels were in close agreement, and dose level appeared to have no influence on study outcomes for either IM or IV administration. The results demonstrate that IM and IV administration of rHA is well tolerated, with no treatment-related serious adverse events and no evidence of an immunological response. The adverse event profile was as expected for healthy volunteers receiving IM or IV administrations of albumin, and there were no apparent dose-associated changes in tolerability. Moreover, there were no safety or pharmacokinetic/pharmacodynamic differences between rHA and HSA over the range of investigated doses. The nature of adverse events recorded, both overall and treatment related, was very similar among recipients of rHA or HSA. There were no significant between-group differences in the incidence of potentially allergic or serious adverse events.

The present studies provide valuable information on the safety profile of rHA compared to HSA, which has been used as an excipient for many biological and biotechnologically derived pharmaceutical products over the past 15 years. The maximum amount of HSA excipient in an already marketed product is 16.5 mg (IM administration).¹⁹ By administering doses that were more than 3.5-fold (IM route) and 3000-fold (IV route) higher than this, the present clinical investigations demonstrate large safety margins for the use of the recombinant human albumin as an excipient.

A variety of analytical methods have previously demonstrated rHA to be structurally equivalent to HSA.² Against this background, the results of the present rHA studies, demonstrating similarity with HSA, are not unexpected. However, as with all products of genetic engineering using *S. cerevisiae* cells, there is a potential for rHA to contain some level of yeast-derived impurities,¹⁶ which may have the capacity to elicit a possible allergic response. In addition, potential differences in glycosylation profiles (mannosylation) of rHA compared to HSA raise the possibility of neoantigens. This was the basis for investigating the potential for an immune response to rHA and its potential impurities. The lack of clinically relevant changes in IgG or IgE indicates no propensity for an immunologic reaction to the rHA product, even in subjects with RAST-positive results to yeast. Given the high doses administered, the demonstration of clinical tolerability is not trivial¹⁶ and reflects the fact that levels of yeast-derived impurities and mannosylated rHA in the test product are extremely low; this is attributable to the high degree of purification and the choice of yeast production strain. In addition, the studies sup-

port preclinical neoantigenicity studies, which showed no evidence of neoantigens in the recombinant human albumin compared to HSA (data not shown).

The present clinical program provides the first direct evidence for the potential to use highly purified rHA in both IM and IV clinical settings, whereas previous data indicate the structural and physical similarity of the recombinant product with native HSA.^{2,16} Although the studies were designed to assess the safety and tolerability of rHA as an excipient for pharmaceutical and biological products, the data indicate that rHA could be developed for all medical applications in which HSA is currently used. In this context, the effective distribution of infused rHA beyond the central plasma compartment becomes particularly important (the maximum albumin increase of 7 g/L after the 50-g IV dose indicates that this is the case).

In summary, the clinical studies described in this article demonstrate that the investigated recombinant human albumin is a suitable non-human- or animal-derived alternative to HSA for excipient and therapeutic use. It is as safe and well tolerated as HSA for IM and IV administration at a range of doses. There was no evidence of antibody production against rHA or its impurities, and this is believed to be attributable to the high degree of purification of the rHA product and the choice of yeast production strain.

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