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Original research

Rice-derived recombinant human serum albumin as an alternative to human plasma for patients with decompensated liver cirrhosis: a randomised, double-blind, positive-controlled and non-inferiority trial

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ABSTRACT

Background Despite inadequate supply and potential contamination risk, human plasma has remained the only source for human serum albumin (pHSA) intravenous administration since the 1940s.

Objective We sought to establish the safety and efficacy of OsrHSA, a recombinant HSA from bioengineered *Oryza sativa* (rice).

Design In this multicentre, randomised, double-blind and positive-controlled study, patients with decompensated liver cirrhosis and serum albumin ≤ 30 g/L were recruited from 22 centres in China. The patients were randomly assigned to OsrHSA or pHSA (4:1) to once-daily intravenous injection (10 g or 20 g) until their serum albumin level reached 35 g/L, for a maximum of 2 weeks, with 2 weeks of follow-up. The primary outcome was the proportion of patients to reach a serum albumin level of 35 g/L (non-inferiority margin < -0.20). Outcomes were evaluated in patients who received the study drug and had at least one post-baseline serum albumin value (full analysis set, FAS). Safety was evaluated in all patients who received the study drug.

Results Between 22 March 2021 and 2 June 2022, 220 patients received OsrHSA (n=175) or pHSA (n=45). 216 patients were included in the FAS (OsrHSA, n=171; pHSA, n=45). Primary outcome of OsrHSA (130/171, 76%) was non-inferior to pHSA (34/45, 75.6%) (difference=0.5%; lower limit of 97.5% CI=-0.119). There was no significant difference between all secondary outcomes of OsrHSA and pHSA. There were no drug-related serious adverse events.

Conclusions Rice-derived HSA is non-inferior to plasma-derived HSA in efficacy and safety. This finding should be confirmed in phase 3 trial.

Trial registration number NCT04835480.

INTRODUCTION

Human serum albumin (HSA) is the most abundant protein (35–50 g/L) in the human plasma and

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a supply shortage for plasma-derived human serum albumin, especially in developing countries. Despite numerous attempts, recombinant albumin had not yet succeeded as a direct substitute for plasma-derived albumin.

WHAT THIS STUDY ADDS

⇒ This study is the first double-blind, randomised and positive-controlled study that compared the safety and efficacy of recombinant albumin with blood-derived albumin in patients receiving repetitive large-dose injections. It is also the first report of any rice-derived recombinant protein in clinical trials. In this US Food and Drug Administration and China Center for Drug Evaluation-regulated study, rice-derived albumin is found to be non-inferior to plasma-derived albumin in efficacy and safety.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study shows that a mass-produced recombinant albumin could potentially replace plasma-derived albumin. Mid-to-low-income countries could use this green and low-cost recombinant technology to address local albumin shortage, achieve affordability and eliminate potential contamination risks from human plasma.

maintains plasma osmotic pressure.¹ Clinically, HSA is widely used to treat diseases including hypovolaemia, shock, burns, surgical blood loss, trauma, haemorrhage, liver diseases and hypoalbuminaemia.^{2,3} Human plasma has been the only source of HSA for intravenous injections since its first clinical use in World War II, despite the call by multiple regulatory agencies to minimise human-derived pharmaceuticals.⁴ Although the human

plasma fractioning process had been improved recently, infections via blood products still occur at an alarming rate, especially in low-income countries.⁵ In mid-income countries, better hospital care and higher income lead to a steadily increasing demand for HSA. However, local blood donation does not meet the increased demand for plasma-derived human serum albumin (pHSA), resulting in limited access for patients.⁶ Because of the higher price sold in high-income countries, pHSA was not allocated preferentially to mid-or-low-income countries, who face chronic shortages. Even in high-income countries with sufficient supply, human plasma supply can dwindle quickly while demand peaks suddenly, as exemplified by the COVID-19 pandemic.⁷ Additionally, certain religious groups reject the use of blood products.⁸

Despite decades of technological advances in recombinant biological pharmaceuticals, recombinant HSA (rHSA) expressed in conventional systems such as yeast or mammalian cells has not been successfully commercialised for direct intravenous injections for three major reasons.⁹ First, since HSA is administered in large doses (10–50 g), rHSA requires an extremely high purity (>99.9999%, measured by amount of impurities, also called host cell protein, HCP).¹⁰ This stringent purity requirement significantly increases the underlying cost, which makes rHSA unaffordable.¹¹ In contrast, 95% purity is acceptable for pHSA because the impurities are from humans and considered safe. Second, yeast-derived or cell line-derived rHSA usually includes non-ionic detergent as a stabilising excipient, which impacts its safety profile at a high dose.^{12–13} Third, current recombinant protein facilities cannot satiate a global yearly shortage of >1000 metric tons of HSA, especially when this requires massive investment into a commercially uncompetitive product.¹⁴

Recombinant HSA derived from rice endosperm (grains) of *Oryza sativa* (OsrHSA) is a safe, cost-effective and reliable source to meet the medical needs of patients worldwide. Compared with pHSA, OsrHSA poses no risk of human pathogens inherently associated with human plasma. Since rice has been a human food staple for thousands of years, rice proteins are orally tolerated and pose lower immunogenicity risk than yeasts or animal cell lines. Rice endosperm only contains four types of storage proteins.¹⁵ These storage proteins are mostly water-insoluble, which makes purification of soluble human proteins simpler.¹⁶ Additionally, large-scale rHSA-expressing rice could be grown without significant capital investment, heavy industrial pollution or intense energy use.^{15–17} Therefore, rice-derived rHSA is especially suitable for low-income to mid-income countries to achieve self-sufficiency in local albumin supply.

Since this was the first rice-derived recombinant protein directly used for intravenous injections in humans, regulatory agencies from both the USA and China required stringent quality control procedures for the production of HSA in rice, as well as the final drug product. The bioengineered rice was grown according to good agriculture practice and met biosafety regulations by the Ministry of Agriculture. The soil and water used in the rice paddy were tested for heavy metals and other contaminants during the entire growing process. All pesticide and herbicide residues were tested following harvest. The drug formulation of OsrHSA was the same as pHSA, without any trace of non-ionic surfactant that was present in yeast or cell line-derived recombinant proteins. Almost all quality control standards of pHSA were included in the OsrHSA drug product, although with a higher purity. Additional testing showed that any trace of pesticides, herbicides, heavy metals and host cell DNAs was below detection limit. A battery of biochemical, cellular and in vivo assays, including crystallisation structure and cryo-electron microscopy,

was performed to assure that OsrHSA had the same primary, secondary, tertiary structure, post-translational modification and bioactivity as pHSA.

This trial is a proof-of-concept study that examined the safety and efficacy of high-dosage recombinant protein from a first-in-human rice grain-based expression system. After a successful phase 1 trial (ClinicalTrials.gov number, NCT04384523, unpublished), we report results from a USA and China regulated phase 2 (HY1001) trial, which evaluated the safety and efficacy of OsrHSA in patients with hypoalbuminaemia caused by decompensated liver cirrhosis, who received albumin per standard medical guidelines in China.

METHODS

Trial design

HY1001 was a multicentre, randomised, double-blind, positive-controlled, non-inferiority phase 2 trial conducted at 22 centres in China from 22 March 2021 to 2 June 2022 (online supplemental material p3). The trial was conducted in compliance with the International Council for Harmonisation E6 Guideline for Good Clinical Practice and all applicable regulations, with active investigational new drug approvals from the US Food and Drug Administration and China Center for Drug Evaluation. The study protocol was approved by the ethics committees at each centre. IQVIA was the independent contract research organisation that oversaw all clinical operations and data analysis.

Patients

Eligible patients were adults aged between 18 and 80 years old, suffering decompensated hepatic cirrhosis with ascites and a serum albumin level ≤ 30 g/L. Patients with known allergic/adverse reaction to cereal or any food containing cereal including rice, history of a severe allergic reaction to any pHSA component or with positive IgE and IgG against rice proteins at screening; patients who had medical conditions except for hepatic cirrhosis, currently requiring the use of albumin such as paracentesis-induced circulatory dysfunction, large-volume paracentesis (>5 L each time); nephrotic syndrome, hepatorenal syndrome or creatinine $>2 \times$ upper limit of normal, significant cardiopulmonary or structural heart disease, haemodialysis, active upper gastrointestinal bleeding, patients with hepatic encephalopathy Grade 3 or 4; malignant ascites or ascites caused by cancer embolus; and patients with Grade C or D liver cancer according to the Barcelona-Clinic Liver Cancer staging were excluded (see the online supplemental material, p4). All participants provided written informed consent.

Randomisation and masking

Patients were allocated to each of the study cohorts with a stratified randomisation algorithm, which would balance the proportion of patients. The stratification factor was based on the baseline serum albumin level of <28 , and ≥ 28 to ≤ 30 g/L. The study was blinded within each cohort, where the investigators and randomised patients were unaware of the study treatments received to avoid bias during the study. Since OsrHSA and pHSA have different packaging, an interactive voice response system/interactive web response system (IVRS/IWRS) provider conducted randomisation and retained treatment assignment codes. Participants could have been unblinded by the investigator if the participant discontinued from the blinded treatment period or in the event of a medical emergency. A notification was to be sent to the medical monitor on any occurrence of unblinding. A deviation was to be filed if unblinding occurred

for any reason other than those listed above. In the event of an emergency, unblinding could have been requested by the investigator via the IVRS/IWRS system.

Procedures

The trial consisted of a screening period up to 14 days, a maximum of 14 days of treatment and a follow-up period of 14 days. All patients were hospitalised and received a daily intravenous infusion of 10 g or 20 g of OsrHSA (20%, 50 mL) or pHSA (Grifols Albutein, 20%, 50 mL) for up to 14 days. The patients were randomised in a 4:1 ratio (OsrHSA vs pHSA) at 10 g or 20 g dose level, prior to dosing. Patients were first enrolled with a lower dose group (10 g/day OsrHSA or pHSA). The Safety Review Committee would recommend a higher dose (20 g/day OsrHSA or pHSA) based on the safety data from 10 g dose groups. Patients were monitored daily from baseline to end of treatment (EOT). If their serum albumin level reached ≥ 35 g/L, the patients were considered to have completed treatment and then entered the follow-up period. Each patient had three follow-up visits in 2 weeks (see online supplemental material). If the patient developed allergic reactions or fluid overload, treatment was stopped temporarily. The investigator provided healthcare according to the patient's medical condition and determined whether to continue the treatment for the patient later. The schedule of assessment is provided at supplemental material (online supplemental table S2).

Outcomes

The primary outcome was the percentage of patients whose serum albumin reached ≥ 35 g/L at any time up to 14 days and centrally assessed. Secondary outcomes included: time to reach serum albumin ≥ 35 g/L by day 14; change in colloid osmotic pressure; serum albumin changes from baseline to the EOT; the severity of ascites (measured by abdominal circumference and bodyweight); the occurrence and titres of the anti-drug antibodies (ADA) and anti-HCP antibodies; safety profiles (including adverse events (AEs), clinical laboratory evaluations, physical examination, vital signs and ECGs). Any events reported by the patient, any new medical conditions and symptoms, any new abnormal findings on physical examination or laboratory evaluation were recorded as AEs. For immunogenicity assessments, blood samples for ADA or anti-HCP antibodies analyses were collected at screening, pre-dose, post-dose and at the end of study. Additional details on safety and efficacy measurements are provided in the supplemental material (online supplemental table S1).

Statistical analysis

The sample size calculation was based on a non-inferiority study design comparing OsrHSA and pHSA treatment groups in terms of the proportion (%) of patients whose serum albumin reached ≥ 35 g/L on or before day 14 (albumin response rate). A sample size of 88 patients in each of the OsrHSA dose groups and 22 in each of the pHSA dose groups assured statistical power of at least 80.0% to reject the null hypothesis that the treatment groups were not equivalent, in favour of the alternative hypothesis that they were equivalent. This used non-inferiority testing of two proportions at a one-sided 2.5% significance level, using normal approximations and assuming a non-inferiority margin of at least 20%, an expected difference in proportions of 5%, 84% proportion in the pHSA group and 20% dropout rate.

The primary outcome analysis was based on 97.5% (one-sided) stratified Newcombe CI computed based on the difference between the proportion of patients attaining serum albumin

≥ 35 g/L on or before day 14 (albumin response rate) of OsrHSA dose group and the pHSA dose group. The randomisation stratification factor was baseline serum albumin level of < 28 , and ≥ 28 to ≤ 30 g/L. To claim that OsrHSA was non-inferior to pHSA, the lower limit of the CI was required to be > -0.20 in the full analysis set (FAS). If the non-inferiority claim above was made for the 20 g dose group, then the same analysis was to proceed for the comparison between OsrHSA 10 g and pHSA 10 g dose group. In addition to randomisation strata, baseline serum albumin levels: < 25 and ≥ 25 and ≤ 30 g/L were also analysed. Analyses using unstratified Newcombe CI were considered supportive.

For secondary outcome analysis, time to achieve serum albumin levels of ≥ 35 g/L was compared between the two treatment groups using the stratified log-rank test. Time to reach serum albumin levels of ≥ 35 g/L was summarised descriptively using the Kaplan-Meier (KM) method. The KM estimate, along with the corresponding 95% CI was calculated using the Brookmeyer and Crowley method and was provided for the median. Decrease in severity of ascites was analysed using the Cochran-Mantel-Haenszel test to compare the two treatment groups. Change from baseline in serum albumin at EOT was analysed using an analysis of covariance. The correlation between change of serum albumin and change of colloid osmotic pressure was analysed by a scatter plot. Safety and tolerability profile including AEs, changes in safety assessment parameters (vitals, ECGs, clinical laboratory results, the incidence and titre of ADA and anti-HCP antibodies) were listed and summarised. All statistical analyses were performed using SAS Linux V.9.4. Additional details on statistical methods are provided in the online supplemental material (p.16). There is a data monitoring committee. This study is registered with ClinicalTrials.gov (NCT04835480).

RESULTS

Patient characteristics

Of 420 patients screened, 224 were enrolled (figure 1). 112 patients were enrolled and randomly assigned to receive OsrHSA 10 g ($n=88$), pHSA 10 g ($n=22$). On safety evaluation of the 10 g dose group, another 112 patients were enrolled and randomly assigned to receive OsrHSA 20 g ($n=87$) or pHSA 20 g ($n=23$). Of the 224 patients randomised, 220 (98.2%) patients received treatment. Four patients were randomised in error (they were found to be not meeting eligibility criteria) and did not receive treatment. 216 (96.4%) patients were included in the FAS and immunogenicity analysis set (defined as patients who received treatment and had at least one measurement for albumin or antibodies). Four patients (three in OsrHSA 10 g and one in OsrHSA 20 g) received the study drug but withdrew before the first serum analysis and were therefore not included in the FAS and immunogenicity analysis set. 220 (98.2%) patients were included in the safety analysis. 199 (88.8%) patients completed the treatment and 44 patients discontinued the study. Demographics and baseline characteristics were similar across treatment groups at both dose levels (table 1). At baseline, the serum albumin concentration, abdominal circumference and colloid osmotic pressure across treatment groups at both dose levels was similar. Child-Pugh score, Model for End-stage Liver Diseases (MELD) 3.0 score and serum creatinine were also similar. Additional details regarding patient baseline characteristics are provided in the supplemental material (online supplemental table S3 and S4).

Outcomes

Combining all dose groups, OsrHSA was non-inferior to pHSA in the primary endpoint (lower limit of 97.5% CI = -0.119)

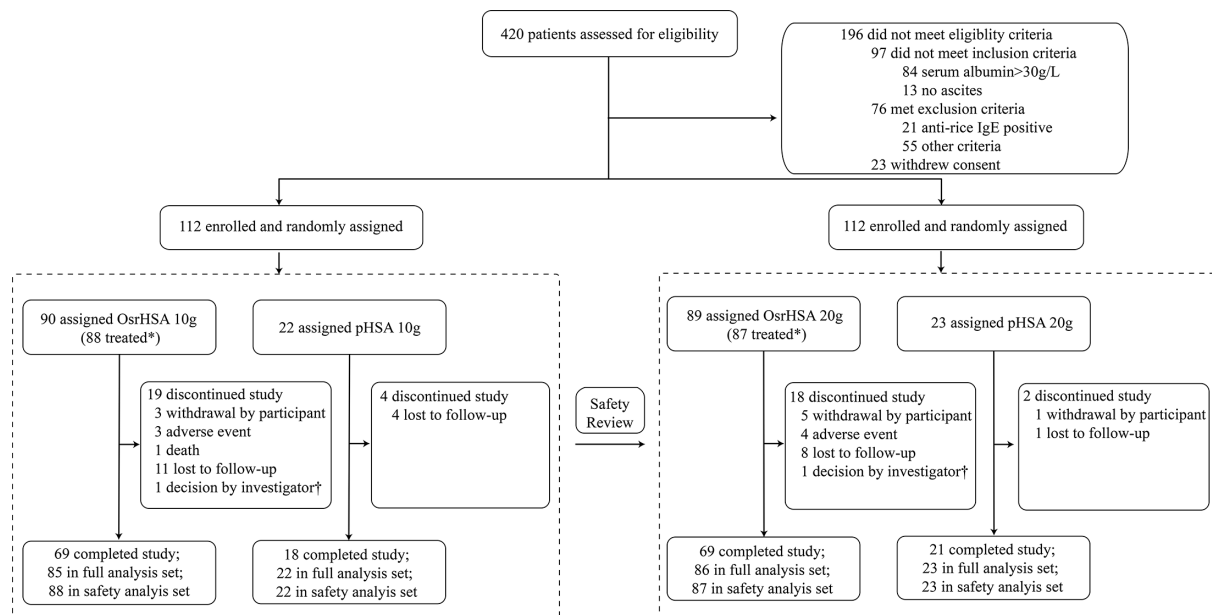


Figure 1 Trial profile. *Four ineligible patients were randomly assigned in error and not treated. †Decision to withdraw is not due to lack of efficacy, but due to error in determining eligibility. Full analysis set is defined as patients who received treatment and had at least one post-treatment measurement for albumin. Four patients (three in OsrHSA 10g and one in OsrHSA 20g) withdrew before serum was collected and were therefore not included in the full analysis set. OsrHSA, *Oryza sativa* recombinant human serum albumin; pHSA, plasma-derived human serum albumin.

in the FAS (figure 2A). By dose level, 10g OsrHSA was non-inferior to 10g pHSA (lower limit of 97.5% CI = -0.114) and 20g OsrHSA was non-inferior to 20g pHSA (lower limit of 97.5% CI = -0.187) (figure 2B). Non-inferiority was also reached in different stratifications (albumin <28 g/L and 28–30 g/L; <25 g/L and 25–30 g/L), per-protocol sets and sensitivity analysis of 20g groups (online supplemental file 1). Serum albumin concentration remained steady for up to 14 days after

EOT, and all groups were similar (figure 1C). Serum creatinine, total bilirubin and MELD 3.0 score did not change after EOT, and all groups are similar (figure 1C).

In all secondary endpoints, there was no statistically significant difference between OsrHSA and pHSA in the FAS (all *p* values exceeded 0.2, table 2). In the 20g dose groups, time to reach the primary outcome was the same (6 days) at 20g dose in both treatment groups. In the 10g dose groups, the median time

Table 1 Baseline characteristics and demographics

	OsrHSA 10g (n=85)	pHSA 10g (n=22)	OsrHSA 20g (n=86)	pHSA 20g (n=23)
Serum albumin (g/L)	26.79 (3.170)	25.45 (3.947)	25.51 (3.531)	26.61 (3.401)
Child-Pugh (score)	9.27 (1.46)	9.25 (1.46)	9.24 (1.57)	9.25 (1.59)
MELD 3.0 (score)	15.18 (3.98)	15.13 (4.05)	15.41 (4.05)	15.38 (4.01)
Colloid osmotic pressure (mm Hg)	17.70 (3.079)	16.65 (2.629)	17.28 (3.752)	17.47 (3.254)
Abdominal circumference (cm)	91.51 (10.632)	90.00 (12.982)	92.97 (10.753)	88.52 (8.550)
Serum creatinine (mg/dL)	0.80 (0.27)	0.84 (0.24)	0.92 (0.38)	0.84 (0.30)
Weight (kg)	65.46 (15.031)	63.54 (13.157)	66.87 (13.079)	64.93 (10.858)
Age (years)	57.6 (10.38)	62.3 (7.85)	57.5 (9.73)	54.7 (9.15)
≥65 years	25 (29.4)	8 (36.4)	23 (26.7)	3 (13.0)
≥75 years	5 (5.9)	1 (4.5)	4 (4.7)	1 (4.3)
Sex				
Male	46 (54.1)	15 (68.2)	62 (72.1)	17 (73.9)
Female	39 (45.9)	7 (31.8)	24 (27.9)	6 (26.1)
Race				
Asian	85 (100)	22 (100)	86 (100)	23 (100)

Full analysis set. Data are mean (SD) or n (%).

MELD, Model for End-stage Liver Diseases; n, number of patients in the relevant category for the treatment group; OsrHSA, *Oryza sativa* recombinant human serum albumin; pHSA, plasma-derived human serum albumin.

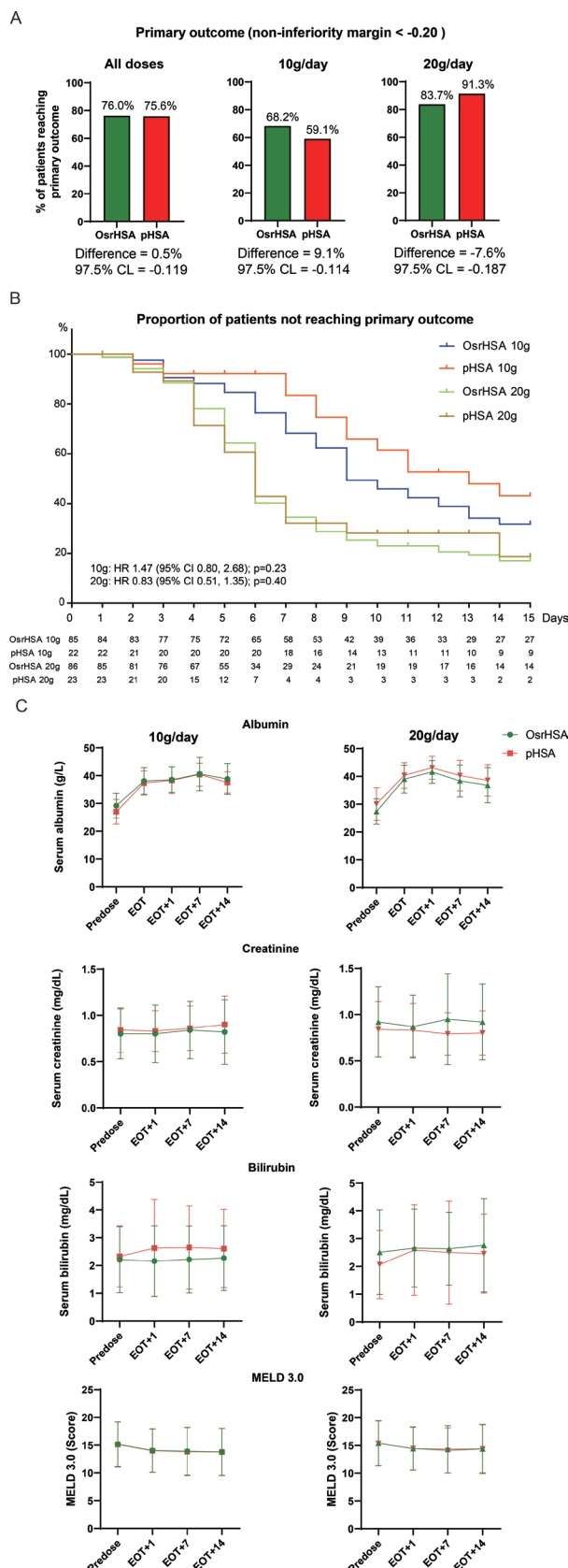


Figure 2 Primary outcome. (A) Non-inferiority analysis of primary outcome in the full analysis set (all doses: OsrHSA, 130/171; pHSA, 34/45; 10g: OsrHSA, 58/85; pHSA, 13/22; 20g: OsrHSA, 72/86; pHSA, 21/23). The adjusted difference and lower 97.5% confidence level (CL) were calculated using Newcombe CI. The non-inferiority margin was 20%. (B) Kaplan-Meier analysis of time to reach primary outcome (full analysis set). (C) Serum albumin, creatinine, bilirubin concentration and MELD 3.0 score from predose to end of follow-up (pharmacokinetic population, defined by patients in the full analysis set who had at least one serum value after EOT). Datapoints are mean and error bars are SD. EOT, end of treatment; MELD, Model for End-stage Liver Diseases; OsrHSA, *Oryza sativa* recombinant human serum albumin; pHSA, plasma-derived human serum albumin.

Table 2 Secondary outcomes

Time to reach serum albumin ≥ 35 g/L (days)	OsrHSA median (95% CI)*	pHSA median (95% CI)*	HR (95% CI)	Log-rank p value
10 g/day	9.0 (9.0 to 12.0)	12.0 (9.0 to NA)	1.47 (0.80 to 2.68)	0.232†
20 g/day	6.0 (NA to NA)	6.0 (4.0 to 7.0)	0.83 (0.51 to 1.35)	0.401†
Change from baseline in serum albumin (g/L)	OsrHSA Adjusted means (SE)	pHSA Adjusted means (SE)	(95% CI)	P value
10 g/day	8.0 (0.4)	7.9 (0.7)	(−1.4 to 1.6)	0.910‡
20 g/day	10.1 (0.5)	11.1 (0.8)	(−2.8 to 0.8)	0.265‡
Change in colloid osmotic pressure (mm Hg)	OsrHSA Adjusted means (SE)	pHSA Adjusted means (SE)	(95% CI)	P value
10 g/day	3.7 (0.4)	3.7 (0.8)	(−1.7 to 1.7)	0.995‡
20 g/day	4.5 (0.4)	5.1 (0.7)	(−2.2 to 0.9)	0.427‡
Decrease in body weight (kg)	OsrHSA Responders n/m (%)	pHSA Responders n/m (%)	(95% CI)	P value
10 g/day	49/85 (57.6)	16/22 (72.7)	(0.151 to 1.558)	0.299§
20 g/day	44/86 (51.2)	15/23 (65.2)	(0.186 to 1.582)	0.333§
Decrease in abdominal circumference (cm)	OsrHSA Responders n/m (%)	pHSA Responders n/m (%)	(95% CI)	P value
10 g/day	42/85 (49.4)	13/22 (59.1)	(0.231 to 1.925)	0.571§
20 g/day	41/86 (47.7)	12/23 (52.2)	(0.300 to 2.329)	0.887§

Full analysis set. A responder is a patient whose body weight improved or abdominal circumference reduced by the EOT period or day 15.

*Brookmeyer and Crowley method was used for median calculation.

†The HR for unstratified analysis was estimated using a Cox proportional hazards model including stratification factor as covariates.

‡Was analysed using an analysis of covariance.

§Was analysed using the Cochran-Mantel-Haenszel test. NA, not applicable or calculable due to rules of the statistical method.

m, number of patients with data available; n, number of treated patients in each group; OsrHSA, *Oryza sativa* recombinant human serum albumin; pHSA, plasma-derived human serum albumin.

to reach the primary outcome was shorter (9 days) for OsrHSA, compared with the 10 g pHSA group (12 days). This difference is not statistically significant, but it could be attributed to a higher serum albumin baseline average in 10 g OsrHSA (26.79) compared with 10 g pHSA (25.75). There was no significant difference between the change from baseline in serum albumin at EOT and the change in colloid osmotic pressure from baseline to EOT, between OsrHSA and pHSA groups. There was no significant difference in the proportion of patients with an improved body weight or abdominal circumference by day 15/EOT across the treatment groups.

Immunogenicity

As a recombinant protein from a first-in-human rice expression system, immunogenicity is of the most important safety concern. We analysed the presence of ADA (table 3). There were no ADA or anti-HCP antibodies increasing beyond sixfold in all patients. No increase in ADA was observed in the 20 g groups. In the 10 g dose groups, 3/85 (3.5%) patients in the 10 g OsrHSA group showed a onefold to fivefold increase in post-treatment ADA titres, compared with 1/22 (4.5%) patients in the 10 g pHSA group. In these cases, the increased ADA values were from a single time point and not observed before or after. The lack of high ADA titre is consistent with the X-ray crystallisation experiment that demonstrated OsrHSA is structurally identical to pHSA.¹⁶

Anti-HCP antibodies did not increase more than fivefold in all patients. In patients with onefold to fivefold increases, anti-HCP antibody values were all single-pass incidence and detected in both OsrHSA (17/117, 9.9%) and pHSA groups (10/45, 22.2%). No relationship was found between the occurrence of adverse

drug reactions or allergy and the results for anti-HCP assays in OsrHSA or pHSA groups in either baseline or post-treatment (table 3 and online supplemental S17). Patient within the OsrHSA group who had allergy-related ADRs of skin symptoms or fever (7/177, 3.9%) were tested negative for anti-HCP. On the other hand, allergy-related ADRs of skin symptoms were noted within the pHSA group (2/45, 4.4%) irrespective of their results for anti-HCP. The lack of high anti-HCP titre is consistent with the HCP ELISA testing showing that OsrHSA is highly pure (99.9999%).¹⁶

Safety

The safety profiles of OsrHSA and pHSA, although with unequal group sizes (4:1), were compared (table 4 and online supplemental S11–S17). First, there were no serious and study drug-related treatment emergent adverse events (TEAEs) in the entire study. Only one patient (0.56%, 1/87) from the 10 g OsrHSA group experienced a fatal TEAE of upper gastrointestinal haemorrhage that was not related to study drug. Infusion-related TEAEs were similar between OsrHSA (4.5%) and pHSA (4.4%). TEAE with more than two incidences or occurring more than 5% was similar between OsrHSA and pHSA (online supplemental table S15 and S16). The proportion of patients experiencing any TEAE was similar across treatment groups (OsrHSA, 116/177, 66.3%; pHSA, 30/45, 66.7%).

In unrelated TEAEs, OsrHSA had a higher incidence of severe or serious TEAE compared with pHSA (severe: OsrHSA, 10.7%; pHSA, 4.4%; serious: OsrHSA, 7.3%; pHSA, 2.2%) (online supplemental table S11 and S12). However, these serious AEs were randomly spread out between different system organ classes. Fever was observed in the OsrHSA group (7.9%) at a

Table 3 Anti-drug and anti-HCP antibodies

ADA	OsrHSA All doses (n=171)	pHSA all doses (n=45)	OsrHSA 10 g (n=85)	pHSA 10 g (n=22)	OsrHSA 20 g (n=86)	pHSA 20 g (n=23)
1-fold to 5-fold increase	3 (1.8)	1 (2.2)	3 (3.5)	1 (4.5)	0	0
6-fold to 10-fold increase	0	0	0	0	0	0
>10-fold increase	0	0	0	0	0	0
+ to +	1 (0.6)	0	1 (1.2)	0	0	0
– to +	8 (4.7)	0	2 (2.4)	0	6 (7.0)	0
Anti-HCP						
1-fold to 5-fold increase	17 (9.9)	10 (22.2)	10 (11.8)	4 (18.2)	7 (8.1)	6 (26.1)
6-fold to 10-fold increase	0	0	0	0	0	0
>10-fold increase	0	0	0	0	0	0
+ to +	23 (13.4)	9 (20)	12 (14.1)	4 (18.2)	11 (12.8)	5 (21.7)
– to +	0	1 (2.2)	0	1 (4.5)	0	0
Visit	OsrHSA Anti-HCP positive at baseline (n=39)	OsrHSA Anti-HCP negative at baseline (n=136)	P value (Fisher)	pHSA Anti-HCP positive at baseline (n=14)	pHSA Anti-HCP negative at baseline (n=31)	P value (Fisher)
ADR overall	3 (7.7)	15 (11)	0.77	1 (7.1)	3 (9.7)	1
Skin	0	5 (3.7)	0.59	1 (7.1)	1 (3.2)	0.53
Respiratory	0	0	1	0	0	1
Fever	0	2 (1.5)	1	0	0	1
Anaphylactic shock	0	0	1	0	0	1

Immunogenicity analysis set included all patients in the full analysis set who had at least one post-dose immunogenicity sample collected to allow estimation of the immunogenicity parameters. Data are n (%). Percentages are based on the number of treated patients in each group. Baseline is the latest available record among screening (day –14 to –2) and screening (day –1).

ADA, anti-drug antibodies; ADR, adverse drug reactions; HCP, host cell proteins; OsrHSA, *Oryza sativa* recombinant human serum albumin; pHSA, plasma-derived human serum albumin; ‘–’ to ‘+’, means that negative at baseline and positive at subsequent visits; ‘+’ to ‘+’, means that positive at baseline and subsequent visits.

Table 4 Summary of adverse events

TEAE category System Organ Class	OsrHSA All doses (n=175)	pHSA All doses (n=45)	OsrHSA 10 g (n=88)	pHSA 10 g (n=22)	OsrHSA 20 g (n=87)	pHSA 20 g (n=23)
Serious and study drug-related TEAE	0	0	0	0	0	0
TEAE leading to death	1 (0.57)*	0	1 (1.1)	0	0	0
Infusion-related TEAE	8 (4.6)	2 (4.4)	4 (4.5)	0	4 (4.6)	2 (8.7)
TEAE $\geq$ 2 incidences	18 (10.3)	4 (8.8)	10 (11.4)	0	8 (9.2)	4 (17.4)
Any TEAE	116 (66.2)	30 (66.7)	63 (71.6)	18 (81.8)	53 (60.9)	12 (52.2)
Severe TEAE	19 (10.8)	2 (4.4)	8 (9.1)	1 (4.5)	11 (12.6)	1 (4.3)
Serious TEAE	13 (7.4)	1 (2.2)	3 (3.4)	0	10 (11.5)	1 (4.3)
Gastrointestinal disorders	4 (2.3)	0	1 (1.1)	0	3 (3.4)	0
Nervous system disorders	4 (2.3)	0	0	0	4 (4.6)	0
Infections and infestations	1 (0.57)	1 (2.2)	1 (1.1)	0	0	1 (4.3)
Metabolism and nutrition disorders	1 (0.57)	0	0	0	1 (1.1)	0
Neoplasms (benign, malignant or unspecified)	1 (0.57)	0	0	0	1 (1.1)	0
Renal and urinary disorders	1 (0.57)	0	1 (1.1)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.57)	0	1 (1.1)	0	0	0
Vascular disorders	1 (0.57)	0	0	0	1 (1.1)	0
TEAE leading to discontinuation of study drug	7 (4.0)	0	3 (3.4)	0	4 (4.6)	0
Gastrointestinal disorders	3 (1.7)	0	1 (1.1)	0	2 (2.3)	0
Skin and subcutaneous tissue disorders	3 (1.7)	0	2 (2.3)	0	1 (1.1)	0
General disorders/administration site conditions	1 (0.56)	0	1 (1.1)	0	0	0
Nervous system disorders	1 (0.56)	0	0	0	1 (1.1)	0
Vascular disorders	1 (0.56)	0	0	0	1 (1.1)	0
TEAE related to serum chemistry laboratory						
Blood creatinine increased	4 (2.3)	2 (4.4)	3 (3.4)	2 (9.1)	1 (1.1)	0
Blood bilirubin increased	1 (0.56)	0	1 (1.1)	0	0	0

Safety analysis set included all patients who received the study drug. Data are n (%).

*This patient succumbed to upper gastrointestinal haemorrhage 15 days after receiving the first dose.

OsrHSA, *Oryza sativa* recombinant human serum albumin; pHSA, plasma-derived human serum albumin; TEAE, treatment-emergent adverse events.

higher rate than pHSA (4.4%). These fever cases occurred after EOT and included common infections such as COVID-19. Therefore, they were deemed not study-drug related. The OsrHSA group had more TEAEs that led to its discontinuation, as three patients withdrew due to pruritus, rash or dermatitis (online supplemental table S13). OsrHSA group also had 1 (0.57%) incidence of infusion site reaction compared with none in the pHSA group (online supplemental table S20). Interestingly, in TEAE with more than one occurrence or 5%, skin disorders highly indicative of allergy, such as pruritus, rash, urticaria and dermatitis, were actually higher in pHSA (4.4%) than OsrHSA (2.8%). Additional details about TEAEs related to serum laboratory and urinalysis results, injection site reactions are provided in the supplemental material (online supplemental table S18-S20). Overall, the risk profile of OsrHSA is controllable and acceptable.

DISCUSSION

This first-in-human study reports the clinical safety and efficacy data of recombinant HSA produced from rice endosperm, and provides preliminary evidence that the rice endosperm cell is a promising pharmaceutical bioreactor to produce functional and safety biopharmaceuticals. Pharmacokinetic analysis of the study drug indicated that albumin serum concentration remained stable after EOT. Consistently, overall albumin concentration is correlated with colloid osmotic pressure in both dose groups. Additionally, trough PK samples were collected. Maximum (trough_{max}), minimum (trough_{min}), median (trough_{med}) and average (trough_{avg}) postbaseline trough values were all similar

between OsrHSA and pHSA (online supplemental table S21). A gross estimate of ascites with body weight and waist circumference also supported the notion that OsrHSA provided some clinical benefit. This trial demonstrated that the protein synthesis and modification mechanism in rice endosperm cells is conserved between humans and higher plants.

Our previously published study demonstrated that OsrHSA was structurally and biochemically identical to pHSA.¹⁶ In our preclinical study with animals, we calculated PK from ¹²⁵I-labelled albumin. In primates (*Cynomolgus macaque*), the half-life and the pharmacokinetics of OsrHSA and pHSA were similar (online supplemental figure S1A,B). We also compared OsrHSA and pHSA's binding to human FcRN in vitro with ELISA, and OsrHSA and pHSA have similar binding to FcRN (online supplemental figure S1C). The binding affinity of two small molecule drugs, which bind in high proportion to albumin, warfarin and naproxen was also similar (online supplemental figure S1D). Lastly, albumin can take on two forms, human mercaptalbumin (HMA) or human non-mercaptalbumin (HNA), depending on the redox status of its Cys34.¹⁸ HMA ratio is 70–80% in healthy adults, but decreased in patients with liver/renal diseases and the ageing population.¹⁹ We measured the Cys34 modification status with liquid chromatography mass spectrometry. HMA ratio in OsrHSA was much higher than pHSA (online supplemental table S22). If the HMA ratio is a 'good' clinical biomarker, then this higher ratio of 'fresh' albumin is considered to be beneficial. In rice endosperm, proteins are stored as 'solid-state' in protein bodies of rice endosperm. It is quickly released and purified during the extraction and purification steps in a very short

time (about 36 hours), which are less likely to be oxidised.¹⁶ In comparison, pHSA has a wide range, most likely due to different donor population and longer separation steps.

For high-dose recombinant proteins such as rHSA, the immunogenicity of recombinant protein itself and impurities from host cells is a critical parameter to predict adverse reactions. There was no high (>6-fold) titre of ADA or anti-HCP antibodies in OsrHSA or pHSA groups. In comparison, it is common to observe high-titre or high incidence of ADAs in many approved recombinant antibodies. In this study, ADA or anti-HCP antibody values did not seem to be a good proxy to predict adverse reactions including allergic reactions such as skin conditions or fever. The 4:1 randomisation ratio (study drug to positive control) resulted in a much smaller sample size for pHSA. This design maximised safety data for OsrHSA, while making it more difficult to directly compare the two groups, especially in terms of safety data. Although OsrHSA had slightly more frequent non-drug-related severe/serious AEs, and more study drug-related withdrawals, these adverse reactions were one-pass, non-serious and manageable. A larger patient population without the anti-rice antibodies ineligibility criteria, with a 1:1 OsrHSA:pHSA ratio, is currently underway (NCT06355479) to fully compare the efficacy and safety of OsrHSA.

Although the replenishment of albumin in cirrhotic patients with hypoalbuminaemia is standard medical practice in China, the internationally recommended indications for the use of HSA in cirrhosis were hepatorenal syndrome, large volume paracentesis and spontaneous bacterial peritonitis. A more clinically meaningful 'hard' primary endpoint other than serum albumin concentration could be more informative. However, HSA is meant as a replacement or supportive therapy, and does not treat liver cirrhosis *per se*.²⁰ It is still under intense debate whether long-term albumin use in patients with decompensated liver cirrhosis would impact overall survival.^{21–27} The purpose of this study was not to resolve this debate, but to compare OsrHSA with pHSA side-by-side. In addition, pHSA has been in the clinics before the age of scientific clinical trials, and there were very few published clinical studies on these indications that could guide a rational statistical design of a non-inferiority trial.

For the first time since the 1940s, a recombinant albumin could potentially replace plasma-derived albumin commercially, and provide a safe, affordable and reliable alternative for millions of patients worldwide. The OsrHSA in this trial was produced in a Good Manufacturing Practice-compliant purification facility capable of producing 1.2 million vials yearly. The building and production costs were considerably more cost-effective compared with pHSA. The impurities (measured by HCP content) of OsrHSA were less than 0.0001% after only three steps of chromatography. With an expression level of 20 g OsrHSA per kilogram of brown rice, only 10 000 acres of rice field would be sufficient to produce 300 tons (30 million vials) of OsrHSA and alleviate the chronic shortage in China. Additionally, it could lower the potential risk of plasma contamination and ethical concerns related to plasma donation. Rice grains may become the preferred method to produce therapeutic proteins on a large scale in the future.

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