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Safety, tolerability, pharmacokinetics and pharmacodynamics of a single intravenous dose of SHR-1707 in healthy adult subjects: two randomized, double-blind, single-ascending-dose, phase 1 studies

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Abstract

Background SHR-1707 is a novel humanized anti-Aβ IgG1 monoclonal antibody that binds to Aβ fibrils and monomers to block the formation of Aβ plaques or to promote the microglial phagocytosis of Aβ. Preclinical studies showed that SHR-1707 reduced brain Aβ deposition in 5xFAD transgenic mice. Herein, we conducted two phase 1 studies to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a single intravenous dose of SHR-1707 in healthy adult subjects.

Methods Two randomized, double-blind, single-ascending-dose, phase 1 studies were conducted in China (Study CHN) and Australia (Study AUS). Study CHN consisted of 2 parts. In Part 1, eligible healthy young adults (18–45 years) were sequentially randomized 8:2 to receive SHR-1707 (five cohorts: 2, 6, 20, 40, and 60 mg/kg) or placebo in each cohort; in Part 2, elderly subjects (55–80 years) were randomized 8:4 to receive SHR-1707 (20 mg/kg) or placebo. A similar design was used in Study AUS, but with only healthy young adults enrolled across three dosing cohorts (2, 20, and 60 mg/kg).

Results Sixty-two (part 1/2, $n=50/12$; age range, 18–42/55–63 years) and 30 subjects (age range, 18–42 years) received SHR-1707 or placebo in Study CHN and Study AUS, respectively. In Study CHN, all treatment-related adverse events (TRAEs) were mild, with the most common being transient laboratory abnormalities. In Study AUS, TRAEs

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were mostly mild (1 moderate event each with SHR-1707/placebo); the most common TRAEs with SHR-1707 were dysgeusia and fatigue (8.3% each). In both studies, the exposure of SHR-1707 increased in a slightly greater than dose-proportional manner over the dose range of 2–60 mg/kg in young adults; there was a dose-dependent increase in plasma Aβ42 concentration following SHR-1707 administration compared with the placebo group. The safety and PK and PD profiles of SHR-1707 in the elderly subjects were consistent with the younger counterpart at the same dose level. No ethnic difference in safety, PK and PD of SHR-1707 was observed.

Conclusions A single intravenous dose of SHR-1707 at 2–60 mg/kg was safe and well tolerated in healthy young adult and elderly subjects. The PK and PD profiles are supportive for further clinical development.

Trial registration NCT04973189 (retrospectively registered on Jul.21, 2021) and NCT04745104 (registered on Feb.6, 2021) on clinicaltrials.gov.

Keywords Alzheimer's disease, anti-Aβ monoclonal antibody, Pharmacokinetics, Pharmacodynamics, Clinical trial

Background

Alzheimer's disease (AD) is a progressive degenerative disease of the central nervous system [1, 2]. It usually affects individuals in their late middle age or elderly years and is the fifth leading cause of death among adults aged 65 years and older in the United States [1]. Currently, over 50 million people worldwide have AD or related dementia, and the number is expected to triple by 2050 [3]. The major clinical manifestations of AD are hypomnesia, cognitive impairment, abnormal behavior, and social communication disturbance [1, 2]. AD has a significant detrimental effect on the quality of life of the patients and their care partners, as well as imposing a substantial burden on social and healthcare systems [1]. Conventional treatments for AD are limited to acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, both of which temporarily alleviate disease symptoms, but cannot delay or reverse the progression of disease [4].

The etiology and pathogenesis of AD are complex. The amyloid β (Aβ) hypothesis is the most widely accepted theory regarding the pathogenesis of AD. According to the hypothesis, excessive accumulation of Aβ in the brain causes the formation of Aβ plaques, which results in tau hyperphosphorylation and neurofibrillary tangles and ultimately leads to neuronal death and cognitive impairment [5], and acts as a primary driving event in AD pathology. Consequently, various Aβ-directed therapies have been under development in clinical trials [5, 6]. These agents exert activities by blocking the formation of Aβ plaques or activating microglia to remove various types of Aβ, including monomers, oligomers, protofibrils, insoluble fibrils and plaques [5, 6]. The U.S. Food and Drug Administration (FDA) has recently approved the anti-Aβ monoclonal antibodies (mAbs) lecanemab (targeting protofibrils) and donanemab (targeting plaques) for the treatment of AD [7, 8]; on the other hand, development of aducanumab (targeting oligomers and fibrils) has been discontinued after its accelerated approval by FDA [9]. There remains an urgent unmet medical need for effective treatments targeting the underlying pathology of AD.

SHR-1707 is a novel humanized anti-Aβ IgG1 mAb that binds to Aβ fibrils and monomers to block the formation of Aβ plaques or to promote the microglial phagocytosis of Aβ. In preclinical studies, SHR-1707 reduced brain Aβ deposition in 5xFAD transgenic mice model of AD, with no safety signals identified (data on file with Hengrui). Herein, we conducted two phase 1 studies to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a single intravenous dose of SHR-1707 in healthy adult subjects of varying age and ethnicity.

Methods

Study design and participants

Two randomized, double-blind, single-ascending-dose, phase 1 studies were conducted concurrently in China (Study CHN; NCT04973189) and Australia (Study AUS; NCT04745104). Study CHN consisted of two parts, with Part 1 involving healthy young subjects aged 18–45 years and Part 2 involving healthy elderly subjects aged 55–80 years. For the elderly cohort, participants were required to have no medical conditions that could substantially impact the administration of the investigational agent or pose additional health risks. They were also expected to maintain stable health throughout the trial without requiring medical intervention. Additionally, subjects had to show no evidence of clinically significant lesions on brain MRI during screening (mandatory assessment). In Study AUS, only healthy young adults aged 18–45 years were enrolled. In both studies, the primary objective was to assess the safety and tolerability of a single intravenous dose of SHR-1707. The secondary objectives were to assess the PK and PD properties of SHR-1707 after a single-dose administration.

The studies were performed in accordance with the ethical principles of Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The study protocol was approved by the institutional review board of the Second Affiliated Hospital of Anhui

Medical University (China) and the Bellberry Human Research Ethics Committee (Australia). All participants provided written informed consent.

Treatments

In Study CHN Part 1, eligible subjects were enrolled into five sequential dosing cohorts (2, 6, 20, 40 and 60 mg/kg), each comprising ten participants. Within each cohort, subjects were randomized in an 8:2 ratio to receive a single intravenous dose of SHR-1707 or matching placebo (Fig. 1A); among them, two sentinel subjects (one each in the SHR-1707 and placebo group) were dosed first to monitor possible adverse events (AEs). Once the dose level was deemed to be safe and well tolerated by the investigator and sponsor through 48 h after dosing, the remaining 8 subjects were enrolled and randomized (7:1). The randomization sequence was generated by a third party and loaded into the randomization and trial supply management system. Subsequent dose escalation for each cohort was determined by the sponsor and investigator, taking into account the safety data 1-week post-dose (given the low risk of amyloid-related imaging abnormalities [ARIAs] in healthy subjects, acute toxicities were prioritized for evaluation for dose escalation) and the PK results. Dose escalation would be terminated if ≥1 subject reported a SHR-1707 related serious AE, or ≥2 subjects reported SHR-1707 related severe AEs in same organ/tissue, or ≥50% subjects reported SHR-1707 related moderate or severe AEs in a dose cohort. After the entire 20 mg/kg cohort in Part 1 completed the 1-week post-dose safety assessment, Part 2 of the study was initiated, with eight subjects randomized to receive a single intravenous dose of SHR-1707 and four to receive placebo; similar to Part 1, two sentinel subjects, one in each group, were dosed before others. Study AUS adopted a similar design to Study CHN Part 1, but only enrolled participants in three dosing cohorts (2, 20, and 60 mg/kg). The safety monitoring committee decided to skip the intermittent dose levels of 6 and 40 mg/kg based on the safety and tolerability results from matched dose levels in Study CHN (Fig. 1B). The maximum escalation dose level was pre-defined as 80 mg/kg in both China and AUS studies, based on the exposure of SHR-1707 under no observed adverse effect level in toxicity studies in cynomolgus monkeys and Sprague Dawley rats. During Study CHN, the actual human exposure of SHR-1707 was

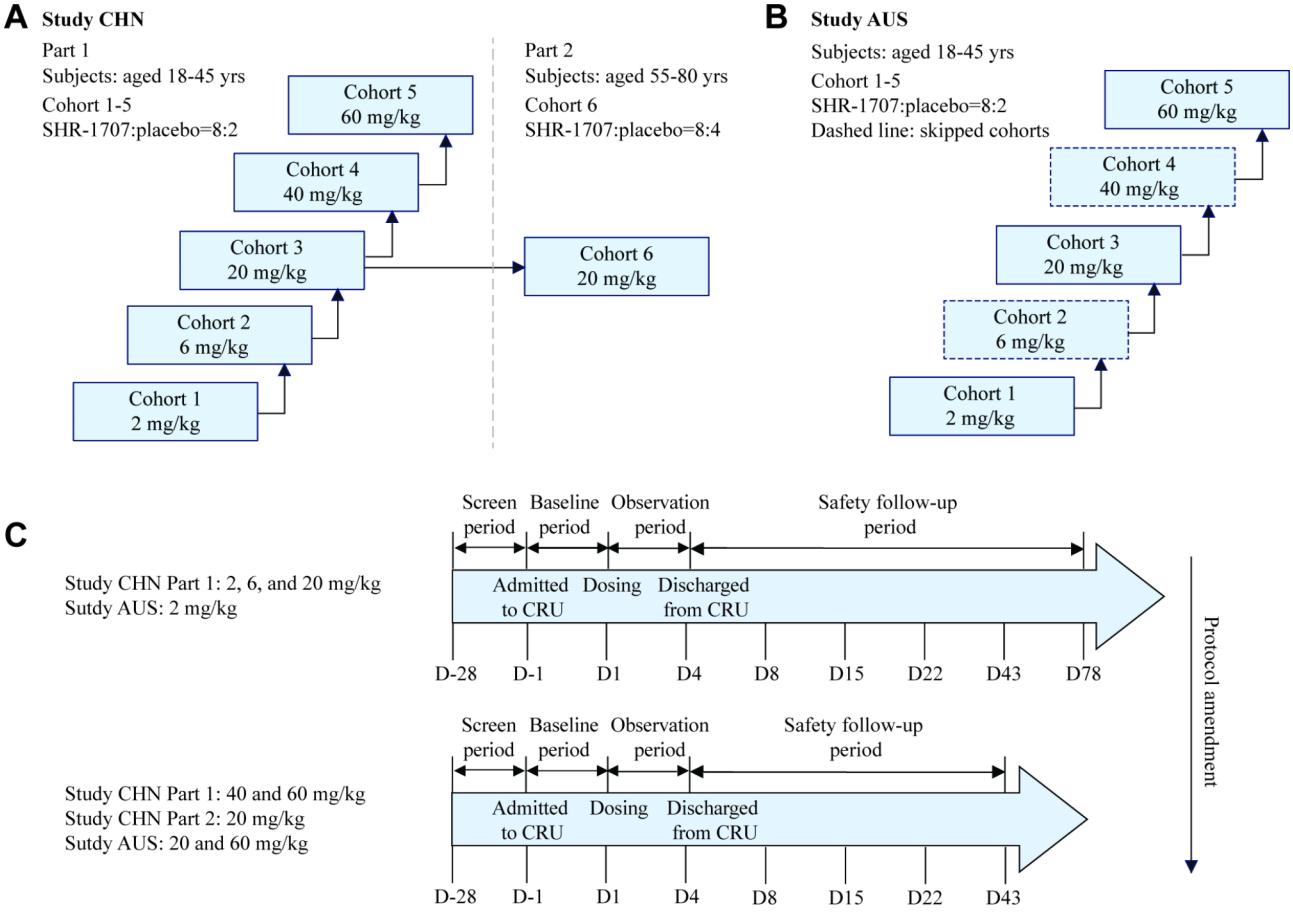

Fig. 1 Overall study design. (**A**) Study design for Study CHN. (**B**) Study design for Study AUS. (**C**) Study visit schema. CRU, clinical research unit; D, day

found to be higher than initially predicted, and the maximum escalation dose level was decreased to 60 mg/kg based on the PK results of previous dose cohorts. In both studies, participants would be withdrawn from the study/discontinued investigational agent under the following conditions: withdrawal of informed consent, pregnancy, prolonged QTc interval prior to dosing, loss to follow-up, and investigator's decision.

Assessments

During the study, all subjects underwent an onsite observation period (day 1 to day 4) and a follow-up period (day 5 to day 43 or 78) for assessment of safety, PK, PD and immunogenicity after dosing. Follow-up visits (days 8, 15, 22, 43 and 78) were conducted up to day 78 for the 2, 6 and 20 mg/kg cohorts in Study CHN Part 1 and the 2 mg/kg cohort in Study AUS. For all subsequent cohorts in the two studies, follow-up was done until day 43 per protocol amendment (Fig. 1C). The decision to decrease the follow-up time to 43 days was based on the shorter-than-expected elimination half-life observed with SHR-1707 in the lower dosing cohorts. Safety of SHR-1707 was monitored during the study using AE records, laboratory tests, vital signs, physical examinations, and 12-lead electrocardiographs (ECGs). For PK analysis, blood samples were collected pre-dose (within 60 min), and 0, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, 48 and 72 h, and 8, 15, 22, 43 and 78 (if applicable) days after the completion of drug infusion; for PD analysis, blood samples were collected pre-dose (within 60 min), and 0.5, 1.5, 3, 8, 24, 48 and 72 h, and 8, 15, 22, 43 and 78 (if applicable) days post-dose. In both studies, SHR-1707 was administered intravenously over 90 min and 0 min was defined as immediately after completion of infusion. The concentration of SHR-1707 was measured in serum using a validated enzyme-linked immunosorbent assay (ELISA) method and that of Aβ42 were measured in plasma using a validated Quanterix Simoa method. Anti-drug antibodies (ADA) were tested in serum samples (collected at pre-dose, 24 h, and 15, 22, 43 and 78 [if applicable] days post-dose) using electrochemiluminescence.

Statistical analysis

The sample size was based on the regulatory requirements for first-in-human trials and practical considerations, which was aimed to provide adequate preliminary safety, tolerability, and PK data at each dose level. Safety was analyzed in all subjects who received one dose of study drug. PK concentration analysis set (PKCS) and PK parameter analysis set (PKPS) included randomized subjects who received one dose of SHR-1707 and had any available PK concentration and parameter data respectively. Additionally, subjects with abnormal PK profiles were excluded from PKPS. PK parameters were calculated using the non-compartment analysis technique. PD and ADA was analyzed in all randomized subjects who received one dose of study drug and had both baseline and at least one post-baseline assessable data for PD and ADA, respectively.

Results

Subject disposition and characteristics

A total of 62 (Part 1: SHR-1707, $n=40$; placebo, $n=10$; Part 2: SHR-1707, $n=8$; placebo, $n=4$) and 30 (SHR-1707, $n=24$; placebo, $n=6$) healthy subjects were randomized and received SHR-1707 or placebo in Study CHN and Study AUS, respectively. Dose escalation up to the planned maximum dose level of 60 mg/kg (adjusted) was completed in both studies without meeting any predefined stopping criteria. All these subjects in both studies completed the trial and were included in the safety, PD and ADA analysis. In Study CHN, all 48 subjects who received SHR-1707 were included in PKCS and PKPS. In Study AUS, all 24 subjects who received SHR-1707 were included in PKCS and 22 subjects were included in PKPS (one each in the 2 and 20 mg/kg groups was excluded; Figure S1). The baseline characteristics of study participants were generally comparable across the SHR-1707 groups and the matching placebo groups in the two studies (Table 1). All subjects in Study CHN were Asian and 90.0% in Study AUS were Caucasian.

Safety

In Study CHN, 28 (70.0%) subjects receiving SHR-1707 and nine (90.0%) subjects receiving placebo experienced treatment-emergent AE (TEAE) in Part 1. Six (75.0%) and two (50.0%) subjects in SHR-1707 and placebo group respectively experienced TEAE in Part 2 (Table S1). Most AEs were mild in severity in both groups, and no AE led to treatment discontinuation, study discontinuation, or death. One serious AE (ectopic pregnancy) was reported in the SHR-1707 20 mg/kg group (Part 1), which was determined as unlikely related to study drug by the investigator. The incidence of treatment-related AEs (TRAEs) was comparable across subjects receiving SHR-1707 and placebo in the 2 parts of Study CHN (Part 1: 70.0% vs. 90.0%; Part 2, 62.5% vs. 50.0%). There were no moderate or severe TRAEs. In both study parts, the most common TRAEs were transient laboratory abnormalities across the treatment groups (all mild and resolved without treatment; Table 2). There was no apparent trend of dose relationship in the incidence of overall or specific TRAEs.

In Study AUS, all 30 (100.0%) subjects who received SHR-1707 or placebo experienced TEAEs, with the majority being mild in severity. One subject discontinued treatment during the administration of SHR-1707 (20 mg/kg) due to vessel puncture site pain and vessel puncture site swelling. There were no AEs leading

Table 1 Baseline characteristics

	Study CHN				Study AUS	
	Part 1		Part 2			
	Placebo ($n=10$)	SHR-1707 ($n=40$)	Placebo ($n=4$)	SHR-1707 ($n=8$)	Placebo ($n=6$)	SHR-1707 ($n=24$)
Mean age (SD), years	26.2 (6.1)	27.2 (5.9)	56.8 (1.7)	57.4 (2.8)	23.5 (8.5)	26.8 (6.9)
Male, n (%)	8 (80.0)	31 (77.5)	2 (50.0)	4 (50.0)	1 (16.7)	8 (33.3)
Race, n (%)						
Asian	10 (100.0)	40 (100.0)	4 (100.0)	8 (100.0)	1 (16.7)	1 (4.2)
White	0	0	0	0	4 (66.7)	23 (95.8)
Other	0	0	0	0	1 (16.7)	0
Mean weight (SD), kg	64.7 (7.3)	66.1 (10.3)	63.4 (2.5)	61.8 (6.7)	68.9 (12.4)	72.9 (10.7)
Mean BMI (SD), kg/m^2	21.9 (2.5)	23.1 (2.7)	24.6 (2.4)	23.1 (2.5)	22.7 (3.5)	24.5 (3.2)

BMI, body mass index; SD, standard deviation

Table 2 Treatment-related adverse events

	Placebo	SHR-1707					
		2 mg/kg	6 mg/kg	20 mg/kg	40 mg/kg	60 mg/kg	Total
Study CHN Part 1							
Subject No.	10	8	8	8	8	8	40
Any TRAE	9 (90.0)	7 (87.5)	4 (50.0)	8 (100.0)	5 (62.5)	4 (50.0)	28 (70.0)
Moderate or severe	0	0	0	0	0	0	0
Serious TRAE	0	0	0	0	0	0	0
TRAEs occurring in ≥ 2 subjects across all groups							
Protein urine present	3 (30.0)	2 (25.0)	0	3 (37.5)	1 (12.5)	3 (37.5)	9 (22.5)
Alanine aminotransferase increased	2 (20.0)	4 (50.0)	0	2 (25.0)	0	0	6 (15.0)
Blood uric acid increased	1 (10.0)	1 (12.5)	1 (12.5)	3 (37.5)	1 (12.5)	0	6 (15.0)
Blood triglycerides increased	2 (20.0)	1 (12.5)	1 (12.5)	1 (12.5)	0	2 (25.0)	5 (12.5)
Urine leukocyte esterase positive	1 (10.0)	0	1 (12.5)	3 (37.5)	1 (12.5)	0	5 (12.5)
White blood cells urine positive	1 (10.0)	1 (12.5)	0	2 (25.0)	1 (12.5)	0	4 (10.0)
Blood bilirubin unconjugated increased	1 (10.0)	0	0	2 (25.0)	0	0	2 (5.0)
Neutrophil count decreased	0	0	0	0	0	2 (25.0)	2 (5.0)
Red blood cells urine positive	0	0	1 (12.5)	0	0	1 (12.5)	2 (5.0)
Urinary occult blood positive	0	0	1 (12.5)	1 (12.5)	0	0	2 (5.0)
Blood bilirubin increased	1 (10.0)	0	0	1 (12.5)	0	0	1 (2.5)
Blood creatine phosphokinase MB increased	1 (10.0)	1 (12.5)	0	0	0	0	1 (2.5)
Gamma-glutamyltransferase increased	2 (20.0)	0	0	0	0	0	0
Study CHN Part 2							
Subject No.	4	–	–	8	–	–	8
Any TRAE	2 (50.0)	–	–	5 (62.5)	–	–	5 (62.5)
Moderate or severe	0	–	–	0	–	–	0
Serious TRAE	0	–	–	0	–	–	0
TRAEs occurring in ≥ 2 subjects across all groups							
White blood cells urine positive	0	–	–	2 (25.0)	–	–	2 (25.0)
Study AUS							
Subject No.	6	8	–	8	–	8	24
Any TRAE	3 (50.0)	2 (25.0)	–	4 (50.0)	–	3 (37.5)	9 (37.5)
Moderate or severe	1 (16.7)	0	–	1 (12.5)	–	0	1 (4.2)
Serious TRAE	0	0	–	0	–	0	0
TRAEs occurring in ≥ 2 subjects across all groups							
Dysgeusia	0	0	–	1 (12.5)	–	1 (12.5)	2 (8.3)
Fatigue	0	0	–	2 (25.0)	–	0	2 (8.3)

Data are n (%). TRAE, treatment-related adverse event

to study discontinuation, serious AEs or deaths. TRAEs were reported in nine (37.5%) subjects receiving SHR-1707 and three (50.0%) subjects receiving placebo. Among them, one case each in the SHR-1707 20 mg/kg group (4.2%; bradykinesia) and placebo group (16.7%; presyncope) were moderate in severity. The most frequently reported TRAEs were dysgeusia (two [8.3%] subjects with SHR-1707 and none with placebo) and fatigue (two [8.3%] subjects with SHR-1707 and none with placebo). There were no apparent dose-dependent trends among different SHR-1707 dosing groups regarding the incidence of TRAEs.

In both studies, there were no significant findings on clinical laboratory tests, 12-lead ECGs, vital signs, physical examination, or exploratory inflammatory biomarkers. A sensitivity analysis including AE data up to day 45 was performed in both studies and the results showed similar incidence of AEs with the primary analysis on safety data with different follow-up periods.

PK

The mean serum concentration-time profile and PK parameters of SHR-1707 following a single intravenous infusion for Study CHN and Study AUS are presented in Fig. 2; Table 3, respectively. In Study CHN Part 1, SHR-1707 reached the peak concentration with a median T_{max} ranging from 1.5 to 4.4 h. The elimination half-life of SHR-1707 increased slightly along with the elevated dose levels and remained virtually unchanged at higher doses. Systemic exposure of SHR-1707 as measured by C_{max}, $AUC_{0\text{-inf}}$ and $AUC_{0\text{-last}}$ showed slightly greater than dose-proportional increase over the dose range of 2–60 mg/kg. In Study CHN Part 2, the PK profile of SHR-1707 in elderly subjects was similar to that in younger subjects in Part 1 at the same dose level (20 mg/kg; Table 3).

In Study AUS, two of 24 subjects receiving SHR-1707 (one each in 2 mg/kg and 20 mg/kg SHR-1707 groups, respectively) were excluded from PKPS due to abnormal PK profiles that did not follow typical pharmacokinetics of the intravenous administration applied in this study due to incomplete infusion or AEs occurred during SHR-1707 administration. The median T_{max} of SHR-1707 ranged from 2.2 to 3.0 h across the dosing groups. The elimination half-life of SHR-1707 increased slightly along with the elevated dose levels with mean t1/2 of 152, 193, and 237 h at 2, 20, and 60 mg/kg, respectively; the geometric mean clearance were 0.421, 0.212, and 0.201 mL/h/kg, respectively. The systematic exposure of SHR-1707 (C_{max}, AUC_{0-inf}, and AUC_{0-last}) over the dose range of 2–60 mg/kg was comparable to those observed in Study CHN Part 1; the increases in C_{max}, AUC_{0-inf} and AUC_{0-last} for SHR-1707 were in a slightly greater than dose-proportional manner with increasing dose (Table 3).

PD

In both Study CHN Part 1 and Study AUS, plasma Aβ42 concentration dose-dependently increased within a few hours after SHR-1707 administration and declined over time afterwards (Fig. 3). The maximal mean change from baseline in Aβ42 levels by dose group are shown in Table 4. The maximal change occurred approximately at 8 h post-dose in the 2 mg/kg groups and at 24 h post-dose in all other dosing groups.

The trend in plasma Aβ42 concentration induced after SHR-1707 administration in elder subjects in Study CHN Part 2 was similar to that observed in younger subjects in Part 1 at the same dose level.

Immunogenicity

In Study CHN Part 1, three subjects (20 mg/kg, $n=2$; 60 mg/kg, $n=1$) were tested positive for anti-SHR-1707 antibodies after a single-dose administration. No impact of the antidrug ADA activity on safety was observed. In Study CHN Part 2 and Study AUS, no subjects were tested positive for ADA at any sampling time point.

Discussion

Anti-Aβ mAbs targeting different aggregation forms of Aβ have shown distinct plaque-clearing effects and clinical efficacy in the treatment of AD [7–11]. SHR-1707 is a novel IgG1 mAb directed against both insoluble (fibrils) and soluble (monomers) Aβ. We conducted two concurrent phase 1 trials in China and Australia to determine the safety, tolerability, PK and PD of SHR-1707 in healthy subjects of different age and ethnicity.

SHR-1707 was generally safe and well tolerated after a single dose up to 60 mg/kg in healthy adults. In both the CHN and AUS studies, the AEs were mostly mild in severity and there were no serious TRAEs or deaths reported. The frequency of subjects experiencing TRAEs were generally similar across the SHR-1707 and placebo groups in the two studies, and no apparent dose dependency was observed (although dysgeusia and fatigue [two cases each] were only reported in SHR-1707 groups). In addition, no notable differences between SHR-1707 and placebo groups were observed for the laboratory tests, vital signs, physical examination, or 12-ECG results. Given that only healthy subjects were enrolled with single dose of investigational product (IP) administered in these first-in-human studies, no brain MRI scans were performed to assess ARIAs, which are important AEs associated other anti-Aβ mAbs [7, 9, 12–14]. A more comprehensive evaluation of the safety profile of SHR-1707, including ARIAs, will be conducted in our ongoing multiple-dose ascending study (NCT05681819) and phase 2 study (NCT06199037) involving patients with AD.

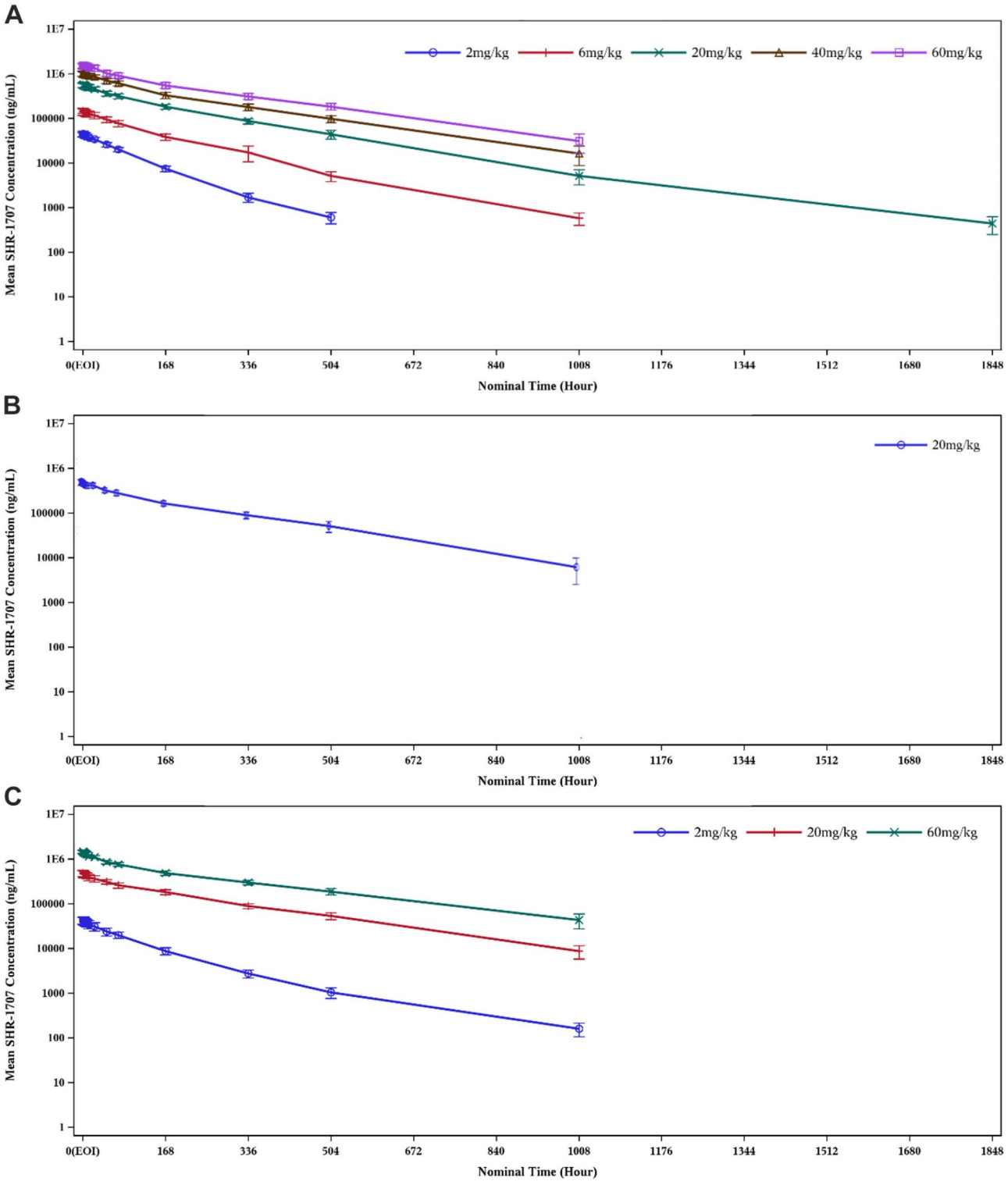

Fig. 2 Mean serum concentration-time curve (semi-log scale) of SHR-1707 after a single intravenous administration. (**A**) Study CHN Part (1) (**B**) Study CHN Part (2) (**C**) Study AUS. Error bars indicate standard deviation. Follow-up was conducted up to day 78 for the 2, 6 and 20 mg/kg cohorts in Study CHN Part 1 and the 2 mg/kg cohort in Study AUS. For all other cohorts in the two studies, follow-up was done up to day 43. EOI, end of infusion

Table 3 Plasma pharmacokinetics of SHR-1707 after a single intravenous administration

	Study CHN							**Study AUS***	
	Part 1					Part 2			
	2 mg/kg (*n* = 8)	6 mg/kg (*n* = 8)	20 mg/kg (*n* = 8)	40 mg/kg (*n* = 8)	60 mg/kg (*n* = 8)	20 mg/kg (*n* = 8)	2 mg/kg (*n* = 7)	20 mg/kg (*n* = 7)	60 mg/kg (*n* = 8)
C_{max}, μg/mL	45.8 (14.4)	148 (13.4)	582 (12.2)	1030 (13.9)	1590 (11.6)	501 (13.0)	43.3 (20.7)	489 (14.3)	1500 (8.4)
AUC_{0-inf}, h*μg/mL	4330 (11)	20,100 (17)	96,000 (14)	190,000 (15)	315,000 (16)	88,500 (16)	4750 (20)	94,600 (11)	299,000 (12)
AUC_{0-last}, h*μg/mL	4270 (11)	19,900 (17)	95,800 (14)	186,000 (15)	306,000 (15)	87,100 (15)	4700 (21)	92,100 (11)	284,000 (10)
$t_{1/2}$, hour	87.3 (33.6)	132 (11.2)	184 (8.2)	193 (14.6)	197 (14.6)	169 (16.9)	152 (21.6)	193 (15.4)	237 (13.0)
CL, mL/h/kg	0.462 (10.8)	0.299 (17.3)	0.208 (13.6)	0.210 (15.1)	0.191 (15.9)	0.226 (15.9)	0.421 (19.7)	0.212 (10.7)	0.201 (11.7)
V_{ss}, mL/kg	51.3 (14.5)	50.5 (15.7)	46.5 (12.5)	51.9 (12.8)	51.1 (11.1)	53.4 (14.1)	64.5 (18.3)	56.2 (17.0)	63.6 (9.2)
T_{max}, hour	1.7 (1.0–4.0)	1.5 (1.0–4.0)	2.5 (1.5-4.0)	1.9 (1.3–3.5)	4.4 (1.4–9.5)	1.5 (1.5–2.5)	3.0 (1.6–3.5)	2.2 (1.7–3.7)	2.2 (1.5–4.5)
MRT, hour	108 (97–148)	168 (147–193)	220 (205–255)	238 (218–296)	267 (234–315)	233 (195–299)	154 (134–177)	277 (216–291)	315 (279–405)

Data are median (range) for T_{max} and MRT, arithmetic mean (coefficient of variation%) for $t_{1/2}$, and geometric mean (geometric coefficient of variation%) for other parameters. Follow-up was conducted up to day 78 for the 2, 6 and 20 mg/kg cohorts in Study CHN Part 1 and the 2 mg/kg cohort in Study AUS. For all other cohorts in the two studies, follow-up was done up to day 43. *Two subjects (one each in 2 mg/kg and 20 mg/kg SHR-17017 groups, respectively) were excluded from PK analysis of PK parameters due to abnormal PK profiles in Study AUS. AUC_{0-inf}, area under the concentration-time curve from 0 h to infinity; AUC_{0-last}, area under the time-concentration curve from time 0 to the last measurable time point; CL, clearance; C_{max}, maximum concentration; MRT, mean residence time; $t_{1/2}$, elimination half-life; T_{max}, time to reach maximum concentration; V_{ss}, volume of distribution at steady state

In Study AUS, two subjects had abnormal PK profiles similar to PK of subcutaneous injection, which may be due to the AE occurrence. One subject in the 2 mg/kg group had venepuncture site oedema leading to IP extravasation; the other subject in the 20 mg/kg group had venepuncture site pain and swelling, resulting in discontinuation of IP administration. Therefore, the PK and PD concentrations of these 2 subjects were not included for analysis. In both CHN and AUS studies, the PK profile of SHR-1707 showed a rapid distribution with a median T_{max} of 1.5–4.4 h across the dose groups following a single intravenous infusion of SHR-1707 at 2–60 mg/kg in healthy adults. The elimination half-life of SHR-1707 increased slightly while the clearance gradually decreased with increasing dose from 2 to 20 mg/kg; both parameters remained relatively stable at the higher dose levels of 20–60 mg/kg. These observations indicated that the clearance route of SHR-1707 might be mainly driven by target-mediated drug disposition (TMDD) at lower dose [15] and proteolysis would take the major role following the saturation of TMDD with the increasing dose level. This hypothesis will require further validation with proper PK modeling in future studies. Notably, the estimated elimination half-life of SHR-1707 was largely similar to the anti-Aβ mAb lecanemab (165 h) and donanemab (223–247 h) [16, 17], but appeared shorter than aducanumab (478 h) at therapeutic doses [18]. The differences might be partly attributed to the variations in the duration of PK sampling period (up to six months post-dose with aducanumab [after a single dose] vs. 28 days for lecanemab and 56 days for donanemab) and the sensitivity of the detection method. Despite the longer estimated elimination half-life with aducanumab, the exposure levels and clearance rates at equivalent doses were generally comparable for SHR-1707 and the other three anti-Aβ mAbs. In terms of systemic exposure, C_{max}, AUC_{0-inf} and AUC_{0-last} of SHR-1707 appeared to increase in a slightly greater than dose-proportional manner for doses ranging from 2 to 60 mg/kg. In general, the rate of ADA positivity was low. Limited by the low incidence of ADA development and single-administration design, further investigation will be necessary to fully understand the impact of ADA on PK and safety.

Aβ mainly presents in two forms, $Aβ_{40}$ and $Aβ_{42}$, with $Aβ_{42}$ being the main component of intracerebral senile plaques [19]. In both studies, following a single intravenous infusion of SHR-1707, plasma $Aβ_{42}$ concentration was dose-dependently increased within a few hours and declined over time with the fall in blood SHR-1707 concentration. This observation could be explained by the affinity of SHR-1707 for monomeric Aβ present in human plasma, which might lead to the removal of soluble plasma $Aβ_{42}$ and result in net efflux of Aβ from the brain to the plasma, and a decrease in the potential tendency of the amyloid plaques deposit in the brain from insoluble fibrils (peripheral sink mechanism [20, 21]). In contrast, plasma $Aβ_{42}$ concentration appeared largely unaffected after a single administration of mAbs with low affinity for soluble/monomeric Aβ (e.g. donanemab and aducanumab), particularly at lower doses [17, 18]. The small sample size of healthy subjects enrolled in our phase 1 studies and individual variations might limit the interpretation of the size effect of SHR-1707 on plasma $Aβ_{42}$ concentrations. Notably, the soluble Aβ-targeted mAbs

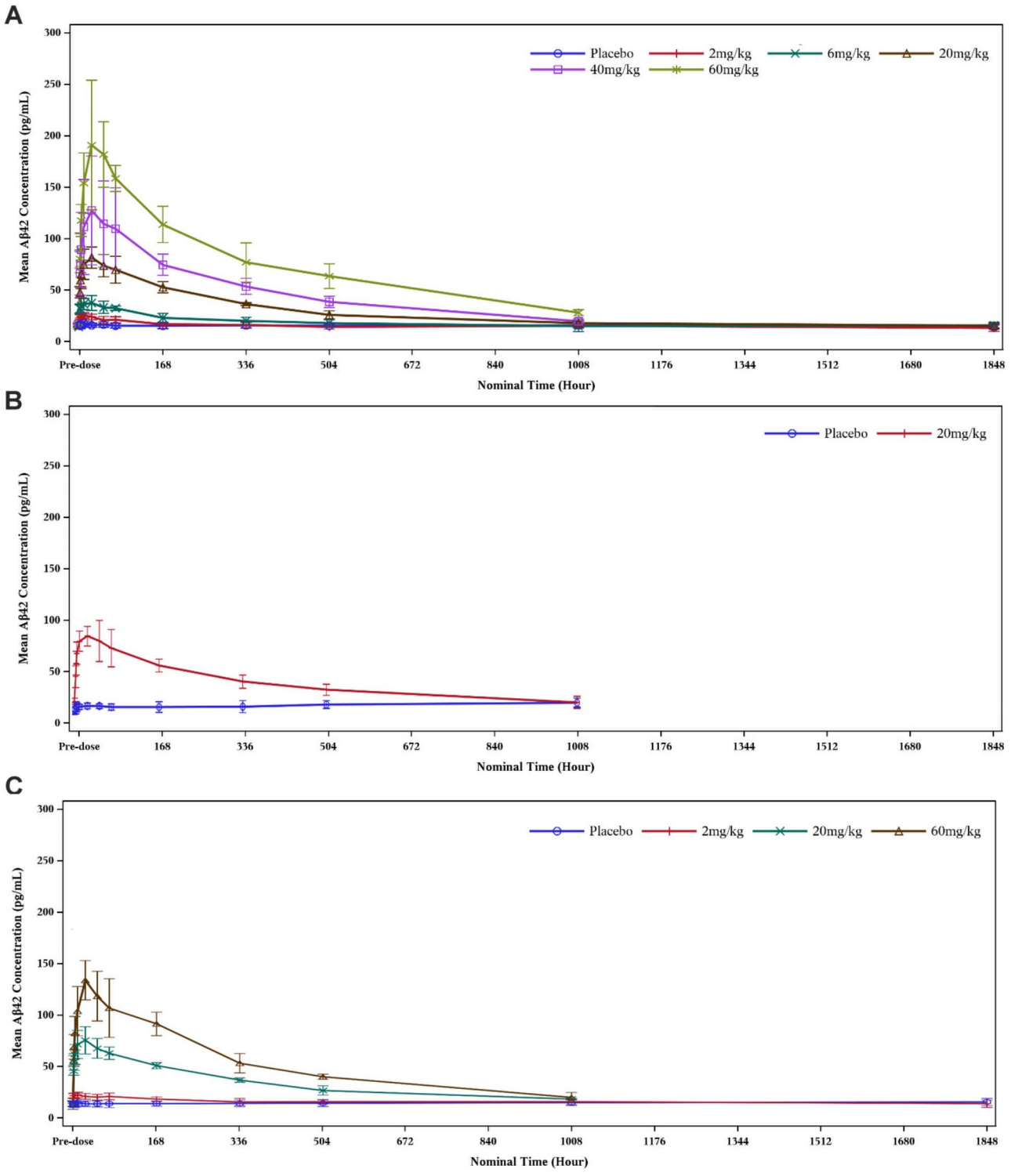

Fig. 3 Mean plasma Aβ42 concentration-time curve after a single intravenous dose of SHR-1707. (**A**) Study CHN Part (1) (**B**) Study CHN Part (2) (**C**) Study AUS. Error bars indicate standard deviation. Follow-up was conducted up to day 78 for the 2, 6 and 20 mg/kg cohorts in Study CHN Part 1 and the 2 mg/kg cohort in Study AUS. For all other cohorts in the two studies, follow-up was done up to day 43

Table 4 Maximal change from baseline in plasma Aβ42 concentration after a single intravenous dose of SHR-1707

	Placebo	SHR-1707*				
		2 mg/kg	6 mg/kg	20 mg/kg	40 mg/kg	60 mg/kg
Study CHN Part 1						
Subject No.	10	8	8	8	8	8
Baseline, pg/mL	16.2 (1.7)	15.4 (1.6)	14.3 (2.4)	15.9 (1.9)	17.5 (0.8)	17.8 (2.0)
Maximal change from baseline, pg/mL	1.3 (2.3)	9.8 (3.6)	23.2 (8.3)	65.6 (10.0)	109.8 (53.2)	173.2 (62.4)
Study CHN Part 2						
Subject No.	4	–	–	8	–	–
Baseline, pg/mL	13.2 (4.8)	–	–	20.1 (4.1)	–	–
Maximal change from baseline, pg/mL	6.7 (7.2)	–	–	64.4 (9.5)	–	–
Study AUS**						
Subject No.	6	8	–	8	–	8
Baseline, pg/mL	14.1 (2.7)	15.0 (1.0)	–	13.7 (2.4)	–	13.9 (5.4)
Maximal change from baseline, pg/mL	1.0 (2.7)	7.6 (2.2)	–	61.6 (13.8)	–	119.5 (17.5)

Data are mean (SD). * Mean Aβ42 maximal change from baseline occurred at 8 h post-dose in the 2 mg/kg groups of SHR-1707 and at 24 h post-dose in other dosing groups of SHR-1707. ** Two subjects (one each in 2 mg/kg and 20 mg/kg SHR-1707 groups, respectively) were excluded from plasma Aβ42 analysis due to abnormal PK profiles in Study AUS

solanezumab and crenezumab showed no improvement in clinical outcomes or reduction in amyloid plaque in phase 3 trials [22, 23]. In the current two studies of SHR-1707, only one form of Aβ (i.e. monomer $A\beta_{42}$) was monitored due to issues with the detection method. Based on our pre-clinical studies, SHR-1707 has shown high binding affinity for various forms of Aβ, potentially distinguishing it from other anti-Aβ mAbs; pharmacodynamic biomarkers related to Aβ will be included for analysis in our subsequent trials of SHR-1707. Furthermore, in our ongoing phase 1b and phase 2 trials involving patients with mild cognitive impairment due to AD or mild AD, we are further characterizing the anti-Aβ effects of SHR-1707 by assessing changes in brain amyloid plaque deposition using Aβ positron emission tomography.

In Study CHN and Study AUS, there were no significant differences in the safety, tolerability, PK and PD profiles across the different age and ethnic groups. Considering that AD is more prevalent in the elderly, the safety and tolerability demonstrated in the elderly subjects could be of particular relevance.

Conclusions

In conclusion, a single intravenous dose of SHR-1707 up to 60 mg/kg was safe and well tolerated in healthy subjects, irrespective of age and ethnicity. The PK and PD profiles are also supportive of further clinical development.

Abbreviations

Aβ	amyloid β
AD	alzheimer's disease
ADA	anti-drug antibody
AE	adverse event
ARIA	amyloid-related imaging abnormality
ECG	electrocardiograph
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
mAb	monoclonal antibody
IP	investigational product
PD	pharmacodynamics
PK	pharmacokinetics
PKCS	pharmacokinetic concentration analysis set
PKPS	pharmacokinetic parameter analysis set
TEAE	treatment-emergent adverse event
TMDD	target-mediated drug disposition
TRAE	treatment-related adverse event

Supplementary Information

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Additional file 1: Figure S1. Trial profile. Table S1. Summary of treatment-emergent adverse events.

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Author contributions

Conceptualization: WH, SS, JWilliams Investigation: WH, SS, JWilliams, YY, YFan, QinZhang, HQin, JWu, XZ, YL, RZ, QianZhang Formal analysis: YX, YFei, XC, FD Project administration: HQiu, JM Supervision: QW, ZY, KS, NL, SF Writing - original draft: YY, HQiu, YX, YFei, XC, FD Writing - review & editing: all authors Approval for submission: all authors.

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Data availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The studies were performed in accordance with the ethical principles of Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The study protocol was approved by the institutional review board of the Second Affiliated Hospital of Anhui Medical University (China) and the Bellberry Human Research Ethics Committee (Australia). All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
HQiu, ZY, JM, YX, SF, YFei, NL, XC, FD, QW, and KS were employees of Jiangsu Hengrui Pharmaceuticals at the time of study. All other authors have no conflicts of interest to declare.

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