Received: 21 December 2023 | Revised: 7 February 2024 | Accepted: 20 February 2024

DOI: 10.1111/cts.13763

ARTICLE

Safety, pharmacokinetics, and pharmacodynamics of anti-IL-4Rα antibody SHR-1819 in healthy subjects: A randomized, controlled phase I study

Na Li[1] | **Sepehr Shakib**[2,3] | **Weilin Qian**[1] | **Xiaoyan Yao**[1] | **Puyuan Li**[1] | **Tsz Keung Nip**[1] | **Xiaoyan Bai**[1] | **Kai Shen**[1]

[1]Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

[2]CMAX Clinical Research, Adelaide, South Australia, Australia

[3]Department of Clinical Pharmacology, University of Adelaide, Adelaide, South Australia, Australia

Correspondence
Kai Shen, Jiangsu Hengrui Pharmaceuticals Co., Ltd., 1288 Haike Road, Shanghai 200000, China.
Email: kai.shen@hengrui.com

Abstract

SHR-1819 is a novel anti-IL-4Rα monoclonal antibody currently under clinical development for use in patients with type 2 inflammatory diseases. In this randomized, double-blind, placebo-controlled, single-dose escalation phase I trial, we evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of SHR-1819 in healthy subjects. Subjects received a single subcutaneous injection of SHR-1819 or placebo, with dose escalation starting at 60 mg and subsequently increasing to 120, 240, 360, and 720 mg. A total of 42 eligible subjects were randomized, and 33 received SHR-1819 (1 subject in the 60 mg cohort and 8 subjects each in the 120, 240, 360, and 720 mg cohorts) and 9 received placebo. SHR-1819 was well-tolerated, with the majority of adverse events being mild in severity. The exposure of SHR-1819 increased in a manner greater than proportionally with a dose range of 120 to 720 mg. The median T_{max} was within 4–7 days (60–720 mg), and the mean half-life ranged from 2.88 to 5.97 days (120–720 mg). The clearance rate of SHR-1819 exhibited a decrease with increasing dose level. Administration of SHR-1819 resulted in a certain degree of reduction in the percentage change from baseline in concentrations of inflammatory biomarkers TARC/CCL17 and IgE, while the reduction of TARC/CCL17 concentrations showed a dose-dependent trend. More than half of the total subjects treated with SHR-1819 were reported antidrug antibody-negative. The preliminary data from this phase I study support further development of SHR-1819 for the treatment of type 2 inflammatory diseases.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

IL-4Rα, a shared receptor subunit for IL-4 and IL-13, plays a pivotal role in the pathogenesis of type 2 inflammatory diseases. Anti-IL-4Rα monoclonal antibodies can inhibit both IL-4 and IL-13 signaling, thus mitigating the inflammatory response associated with type 2 inflammatory diseases. Preclinical studies have

demonstrated that SHR-1819, a novel anti-IL-4Rα monoclonal antibody, has a high affinity for human and marmoset IL-4Rα. It has also shown promising biological activity in hIL-4/hIL-4Rα transgenic mouse models of atopic dermatitis, rhinitis, and asthma.

WHAT QUESTION DID THIS STUDY ADDRESS?

This first-in-human phase I study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of SHR-1819 in healthy subjects.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

SHR-1819 was well-tolerated by the subjects. The exposure to SHR-1819 increased in a greater-than-proportional manner with escalating doses ranging from 120 mg to 720 mg. SHR-1819 led to modest reductions in the concentrations of inflammatory biomarkers TARC/CCL17 and IgE.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides valuable evidence that can guide further clinical development of SHR-1819.

INTRODUCTION

Type 2 inflammatory diseases, such as atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic esophagitis (EoE), and prurigo nodularis, pose significant global health challenges.[1,2] The pathogenesis of these diseases is primarily mediated by Th2 cells that release cytokines such as interleukin-4 (IL-4), IL-5, IL-9, and IL-13, all of which play a pivotal role in driving the inflammatory response.[3] The high worldwide prevalence of these conditions and their substantial impact on quality of life underscore the urgent need for more targeted therapeutic strategies.

The IL-4 receptor alpha (IL-4Rα), a shared receptor subunit for IL-4 and IL-13, plays a crucial role in the pathogenesis of type 2 inflammatory diseases.[4,5] By binding to different subunits, IL-4Rα forms two receptor complexes capable of transmitting downstream signals, thus modulating the immune response. This makes IL-4Rα a promising therapeutic target. Monoclonal antibodies (mAbs) targeting hIL-4Rα can inhibit both IL-4 and IL-13 signaling, offering a more comprehensive approach than drugs that block either the IL-4 or IL-13 pathway alone.[6,7] Anti-IL-4Rα mAbs have the potential to disrupt this pathway, thereby attenuating the inflammatory response associated with type 2 inflammatory diseases.[8–10]

Dupilumab, the frontrunner among anti-IL-4Rα mAbs, has received approval from the US Food and Drug Administration (FDA) for use in patients aged ≥6 years with moderate-to-severe AD,[11–15] as an add-on maintenance treatment in patients aged ≥6 years with moderate-to-severe asthma,[16–18] in adult patients with CRSwNP,[19] in patients aged ≥12 years with EoE,[20] and in adult patients with prurigo nodularis.[21] The promising efficacy of dupilumab in managing type 2 inflammatory diseases further underscores the potential of the therapeutic strategy of anti-IL-4Rα mAbs.

SHR-1819 is a novel monoclonal antibody targeting hIL-4Rα and is currently under clinical development for use in patients with type 2 inflammatory diseases. Preclinical studies have shown that SHR-1819 exhibits high affinity for human and marmoset IL-4Rα and has demonstrated promising biological activity in hIL-4/hIL-4Rα transgenic mouse models of AD, rhinitis, and asthma. The inhibitory activity and receptor occupancy characteristics of SHR-1819 to hIL-4/hIL-4Rα were comparable to those of dupilumab in vitro (data not shown). In this context, we conducted a first-in-human phase I study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of SHR-1819 in healthy subjects.

METHODS

Study design and population

This study was a randomized, double-blind, placebo-controlled, single-dose escalation, single-center phase I trial conducted in Australia (ClinicalTrials.gov, NCT04561128). Healthy subjects aged between 18 and 55 years, with a body mass index ranging from 19 to 35 kg/m^2,were considered eligible. Exclusion criteria included the presence or a history of severe adverse reactions to IL-4Rα antibody drugs and their excipients or

to other biological agents; positive tests for hepatitis B virus (HBsAg), hepatitis C virus (HCV-Ab), human immunodeficiency virus (HIV-Ab), or QuantiFERON-TB Gold; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥2× the upper limit of the normal range (ULN), total bilirubin levels ≥1.5× ULN; and the use of any immunosuppressive agents or anti-interleukin antibody drugs within 6 months prior to screening.

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guideline. All protocols and amendments received approval from the institutional review board or independent ethics committee. All participants provided written informed consent before enrollment.

Procedures

Subjects received a single dose of subcutaneous injection of SHR-1819 or placebo. The dose escalation began with the lowest dose of 60 mg, followed by 120, 240, 360, and 720 mg. The starting dose, dosing frequency, and maximum dose were determined based on animal toxicology data, the receptor occupancy rate in preclinical PK assay, the results of similar drug dupilumab in the first-in-human trial, and relevant FDA guidelines.[22] The study planned to enroll 10 subjects in each dose cohort (8 to receive SHR-1819 and 2 to receive placebo), except for the 60 mg dose cohort which included only 2 subjects (one each to receive SHR-1819 and placebo). In total, 42 healthy subjects were planned to be enrolled in this study. An Interactive Response Technology system was used to randomize subjects and assign them in different dose cohorts. Subjects, investigators, and the sponsor study team were all kept unaware of the treatment subjects received.

Two sentinel subjects (1 for SHR-1819 and 1 for placebo) in each dose cohort were enrolled first and received the assigned treatment. If the dose was deemed safe and well-tolerated by both the investigator and sponsor 48 h post-dose in the sentinel subjects, the remaining subjects were scheduled for dosing. The decision to escalate the dose was made by the Safety Monitoring Committee, based on a review of available safety data (and PK data, if available) up to Day 8 in each cohort. The dose escalation would be terminated and the treatment would be unblinded if any of the following criteria were met for a given dose cohort: occurrence of a serious adverse events (AE) related to SHR-1819; occurrence of severe AE in the same organ system or tissue related to SHR-1819 in ≥2 subjects; or occurrence of moderate or severe AEs related to SHR-1819 in ≥50% of subjects.

The subcutaneous injection of SHR-1819 or placebo was administered at least 3 cm away from the umbilicus on the abdomen. For subjects in the 240–720 mg dose groups, multiple injections were performed at different sites on the abdomen, with each injection site being at least 1 cm away from other injection sites in a clockwise direction. For safety assessment at the injection sites, all injection sites were assessed as a whole per subject. Any AEs occurring at any injection site in a subject were reported by the subjects or investigator during the trial.

Assessments

Subjects were administered with SHR-1819 or placebo subcutaneously on Day 1 and discharged from the Clinical Research Unit on Day 6. Subjects were required to return to the trial center for safety, PK, and PD follow-up on prespecified timepoints until Day 85. Safety including physical examinations, vital signs, 12-lead electrocardiogram, laboratory examinations, and incidence and severity of AE were assessed. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0, and summarized by treatment dose group, severity, and relationship to study treatment based on investigator assessment.

PK samples were collected at the following prespecified timepoints: pre-dose, 12, 24, 48, 72, 96, 120 h, Day 8, Day 11, Day 15, Day 22, Day 29, Day 43, Day 57, and Day 85 post-dose. A volume of 3.5 mL of blood at each timepoint was collected for PK analysis. The serum concentration of SHR-1819 was determined using a validated analytical method of enzyme-linked immunosorbent assay (ELISA) at Frontage Laboratories. The lower limit of quantitation of SHR-1819 was 10.0 ng/mL and the upper limit of quantitation was 200 ng/mL.

Blood samples for PD analysis were collected at predose, Day 8, Day 15, Day 22, Day 29, Day 57, and Day 85 post-dose. A volume of 3.5 mL of blood was collected for the detection of TARC/CCL17, and 2 mL of blood was collected for the detection of IgE at each timepoint. TARC/CCL17 concentrations were analyzed using a validated analytical assay of ELISA at Frontage Laboratories, while IgE concentration was analyzed using the Atellica IM Total IgE assay at the Australian Clinicalabs (ACL) in Australia.

Blood samples for immunogenicity (antidrug antibody, ADA) assessments were collected at pre-dose, Day 8, Day 15, Day 22, Day 29, Day 57, and Day 85 post-dose. A column of 5 mL of blood samples were collected at each timepoint. The anti-SHR-1819 antibody was analyzed using a validated analytical method of Meso Scale Discovery Electrochemiluminescence (MSD-ECL) at Frontage Laboratories.

Outcomes

The primary endpoint was safety, and secondary endpoints were PK, PD, and immunogenicity assessments (ADA).

PK parameters included serum concentration of SHR-1819, area under the concentration–time curve from time zero to time of the last quantifiable concentration after dosing ($AUC_{0\text{-last}}$), area under the plasma concentration–time curve from zero to infinity ($AUC_{0\text{-inf}}$), time to maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), half-life ($t_{1/2}$), apparent total clearance (CL/F), apparent volume of distribution (V_z/F), and mean residence time (MRT). PD parameters included serum thymus and activation-regulated chemokine (TARC/CCL17) level and the percentage change from baseline; serum IgE level and the percentage change from baseline.

Statistical analysis

The sample size was not predetermined by any formal statistical calculation. Safety was assessed in subjects who received at least one dose of study drug. Analysis of plasma concentration of SHR-1819 and PK parameters was performed on subjects who received at least one dose of study drug and had at least one evaluable blood sample for plasma drug concentration and PK parameter assessment. PD parameters and ADA results were evaluated in subjects who had at least one dose of study drug and had pre-dose baseline and at least one post-dose blood sample for evaluation.

Descriptive statistics were used to summarize baseline characteristics, safety data, PK and PD parameters, and ADA results. The area under the curve (AUC) of PK parameters was analyzed using a non-compartment model. Normalized PK parameter ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}) by dose were analyzed using the analysis of variance (ANOVA) model and power model (the SHR-1819 60 mg dose cohort was excluded due to only one subject being treated with study drug). SAS v9.4 (SAS Institute) or above was used to perform statistical analyses and the Phoenix WinNonlin Software Version 8.3 (Certara USA) was used to calculate the PK parameters.

RESULTS

Subjects

Between November 4, 2020 and November 23, 2021, 75 subjects were screened, of which 42 healthy subjects met the eligibility criteria. These subjects were then randomized, with 33 received SHR-1819 (1 subject received 60 mg and 8 subjects received 120, 240, 360, and 720 mg each) and 9 received placebo (Figure 1). All subjects successfully completed their assigned treatment. The demographic data and baseline were well-balanced across different dose groups of SHR-1819 and placebo, except the SHR-1819 60 mg group which had one subject (Table 1). The median age of subjects was 27 (range, 18–54) years and the majority were White (73.8%). The mean (standard deviation) BMI of the study subjects was 27.2 (4.6) kg/m^2. All subjects tested negative for urine drug, breath alcohol, and nicotine prior to dosing.

Safety

The safety analysis set included all 42 subjects. Treatment-emergent adverse events (TEAEs) were reported in 41 subjects (97.6%), which comprised 32 subjects (97.0%) from the SHR-1819 treatment groups and all 9 subjects (100%) from the placebo group (Table 2, Table S1). Most TEAEs were mild in severity (73.8%, 31 of 42), with moderate and severe TEAEs reported in 21.4% (9 of 42) and 2.4% (1 of 42, a left ankle sprain not related to SHR-1819) of the subjects, respectively (Table S2). The incidences of TEAE were 100% (1 of 1), 87.5% (7 of 8), 100% (8 of 8), 100% (8 of 8), and 100% (8 of 8) for the SHR-1819 60, 120, 240, 360, and 720 mg, respectively. No discernible dose-dependent trends were observed among different SHR-1819 treatment groups regarding TEAE incidence.

The most common TEAEs, occurring in at least 10% of subjects in the SHR-1819 groups by preferred term (PT), included injection site reaction (75.8% in the SHR-1819 groups combined vs. 88.9% in the placebo group), headache (33.3% vs. 55.6%), vessel puncture site bruise (30.3% vs. 11.1%), vessel puncture site pain (15.2% vs. 33.3%), upper respiratory tract infection (12.1% vs. 11.1%), and diarrhea (12.1% vs. 11.1%).

Treatment-related adverse events (TRAEs) were reported in 83.3% (35 of 42) of the total population. This included 78.8% (26 of 33) of the subjects in the SHR-1819 groups combined and all 9 subjects (100%) in the placebo group. TRAEs that occurred in at least 10% of subjects in the SHR-1819 groups by PT were injection site reaction (75.8% in the SHR-1819 groups combined vs. 88.9% in the placebo group) and headache (12.1% vs. 22.2%). In different dose groups of SHR-1819 no obvious dose-dependent trend in the incidence of TRAEs was observed. There were no deaths, serious AEs, or any AEs leading to dose reduction or discontinuation during the study.

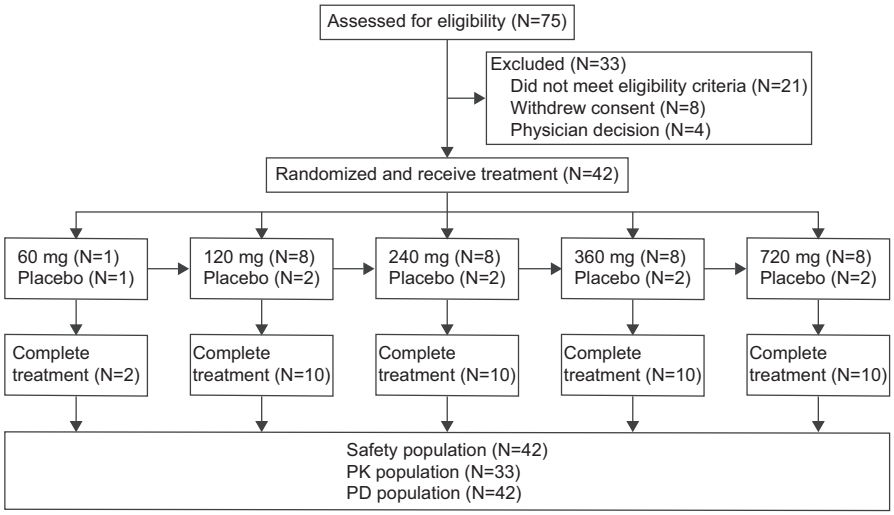

FIGURE 1 Scheme illustrating study participant disposition. PD, pharmacodynamics; PK, pharmacokinetics.

TABLE 1 Demographics and baseline characteristics of the study participants.

Characteristics	60 mg (*N* = 1)	120 mg (*N* = 8)	240 mg (*N* = 8)	360 mg (*N* = 8)	720 mg (*N* = 8)	Placebo (*N* = 9)	Total (*N* = 42)
Age, median (range)	25.0 (25–25)	39.0 (22–52)	29.0 (22–48)	26.0 (21–44)	26.5 (20–33)	24.0 (18–54)	27.0 (18–54)
Sex, *n* (%)							
Male	0	6 (75.0)	4 (50.0)	5 (62.5)	6 (75.0)	4 (44.4)	25 (59.5)
Female	1 (100)	2 (25.0)	4 (50.0)	3 (37.5)	2 (25.0)	5 (55.6)	17 (40.5)
Race, *n* (%)							
White	0	7 (87.5)	4 (50.0)	7 (87.5)	5 (62.5)	8 (88.9)	31 (73.8)
Asian	1 (100)	0	2 (25.0)	0	1 (12.5)	1 (11.1)	5 (11.9)
Black or African American	0	1 (12.5)	1 (12.5)	0	0	0	2 (4.8)
Native Hawaiian or other Pacific islander	0	0	0	0	1 (12.5)	0	1 (2.4)
Unknown	0	0	1 (12.5)	1 (12.5)	1 (12.5)	0	3 (7.1)
BMI, kg/m^2, mean (SD)	34.8	28.5 (2.8)	25.9 (5.6)	24.7 (3.3)	29.2 (4.8)	27.0 (4.7)	27.2 (4.6)
IgE, KU/L							
n	1	6	5	7	8	6	
Mean (SD)	39.0	180 (313)	99.0 (120)	207 (183)	106 (103)	98.7 (130)	
TARC/CCL17, pg/mL							
n	1	8	8	8	8	9	
Mean (SD)	160	230 (166)	208 (75.6)	151 (79.3)	234 (90.2)	260 (137)	

Abbreviations: BMI, body mass index; SD, standard deviation.

PK

The PK concentration and PK parameter analyses were evaluated in the 33 subjects administered with SHR-1819. The concentration–time profiles of SHR-1819 in the serum by dose level are depicted in Figure 2.

Upon administration of a single SHR-1819 dose, ranging from 60 to 720 mg, the median time to peak concentration (T_{max}) was within 4–7 days (Table 3). The mean half-life ($t_{1/2}$) values ranged from 2.88 to 5.97 days across the administered dose range, with the exception of the 60 mg dose level, which had only one subject with a $t_{1/2}$ value of 1.11 days. As the dose increased from 60 to 720 mg, there was a corresponding rise in both the geomean peak drug concentration (C_{max}) and overall exposure ($AUC_{0\text{-inf}}$), ranging from 4.84 to 47.1 μg/mL and 26.9 to 1040 day*μg/mL, respectively. The geomean of total volume of distribution ranged from 3580 to 6870 mL. The clearance of SHR-1819 reduced with increased dose levels, suggesting a nonlinear, target-mediated elimination trend.

The dose proportionality of SHR-1819 was investigated in a dose range from 120 to 720 mg using power model.

TABLE 2 Treatment-emergent adverse events and treatment-related adverse events by preferred term.

Preferred term	60 mg (*N* = 1)	120 mg (*N* = 8)	240 mg (*N* = 8)	360 mg (*N* = 8)	720 mg (*N* = 8)	SHR-1819 (*N* = 33)	Placebo (*N* = 9)
Subjects with at least one TEAE	1 (100)	7 (87.5)	8 (100)	8 (100)	8 (100)	32 (97.0)	9 (100)
Injection site reaction	1 (100)	6 (75.0)	5 (62.5)	5 (62.5)	8 (100)	25 (75.8)	8 (88.9)
Headache	0	5 (62.5)	2 (25.0)	2 (25.0)	2 (25.0)	11 (33.3)	5 (55.6)
Vessel puncture site bruise	1 (100)	1 (12.5)	5 (62.5)	2 (25.0)	1 (12.5)	10 (30.3)	1 (11.1)
Vessel puncture site pain	1 (100)	1 (12.5)	2 (25.0)	1 (12.5)	0	5 (15.2)	3 (33.3)
Upper respiratory tract infection	0	0	2 (25.0)	0	2 (25.0)	4 (12.1)	1 (11.1)
Diarrhea	0	3 (37.5)	0	1 (12.5)	0	4 (12.1)	1 (11.1)
Rhinitis	0	1 (12.5)	0	2 (25.0)	0	3 (9.1)	1 (11.1)
Dermatitis contact	0	1 (12.5)	2 (25.0)	0	0	3 (9.1)	0
Fatigue	0	0	0	0	2 (25.0)	2 (6.1)	2 (22.2)
Vessel puncture site reaction	0	1 (12.5)	0	1 (12.5)	0	2 (6.1)	1 (11.1)
Sunburn	0	1 (12.5)	0	0	1 (12.5)	2 (6.1)	2 (22.2)
Subjects with at least one TRAE	1 (100)	7 (87.5)	5 (62.5)	5 (62.5)	8 (100)	26 (78.8)	9 (100)
Injection site reaction	1 (100)	6 (75.0)	5 (62.5)	5 (62.5)	8 (100)	25 (75.8)	8 (88.9)
Headache	0	2 (25.0)	0	0	2 (25.0)	4 (12.1)	2 (22.2)
Fatigue	0	0	0	0	2 (25.0)	2 (6.1)	1 (11.1)
Dizziness	0	0	0	0	1 (12.5)	1 (3.0)	0
Lethargy	0	1 (12.5)	0	0	0	1 (3.0)	0
Mouth ulceration	0	0	1 (12.5)	0	0	1 (3.0)	1 (11.1)
Abdominal discomfort	0	1 (12.5)	0	0	0	1 (3.0)	0
Diarrhea	0	1 (12.5)	0	0	0	1 (3.0)	0
Macule	0	1 (12.5)	0	0	0	1 (3.0)	0
Rash pruritic	0	0	0	1 (12.5)	0	1 (3.0)	0
Alanine aminotransferase increased	0	0	1 (12.5)	0	0	1 (3.0)	0
Dyspnea	0	0	0	1 (12.5)	0	1 (3.0)	0
Flushing	0	1 (12.5)	0	0	0	1 (3.0)	0
Feeling hot	0	0	0	0	0	0	1 (11.1)
Nausea	0	0	0	0	0	0	1 (11.1)
Vomiting	0	0	0	0	0	0	1 (11.1)

Note: Data are *n* (%). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 25.0). TEAEs occurring in ≥2 subjects in SHR-1819 cohorts and all TRAEs are listed. Events are shown in descending order of frequency in the SHR-1819 group.

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

The results revealed that the slopes of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ against dose were 1.1 (90% CI 0.82–1.29), 1.5 (90% CI 1.18–1.81), and 1.5 (90% CI 1.11–1.83), respectively. This suggests that the C_{max} of SHR-1819 increased in a dose proportional manner and the AUC of SHR-1819 increased in a greater-than-proportional manner with increasing dose within the studied dose range.

PD

The PD analysis was conducted on 42 subjects who were administered with either SHR-1819 or placebo. The TARC/CCL17 concentration decreased from Day 8 to Day 29 following the administration of SHR-1819 in 120, 240, 360, and 720 mg doses, and reverted close to the baseline levels on Day 85 (Figure 3a). The median percentage reduction from baseline in TARC/CCL17 concentrations after SHR-1819 administration showed a dose-dependent trend, with the maximal reduction (−32.1%) observed in the 720 mg dose level on Day 29.

SHR-1819 also led to a modest reduction in IgE concentration across all dose levels (Figure 3b). The median percentage reduction from baseline in IgE concentrations demonstrated a gradual decrease after administering SHR-1819. However, no clear dose-dependent

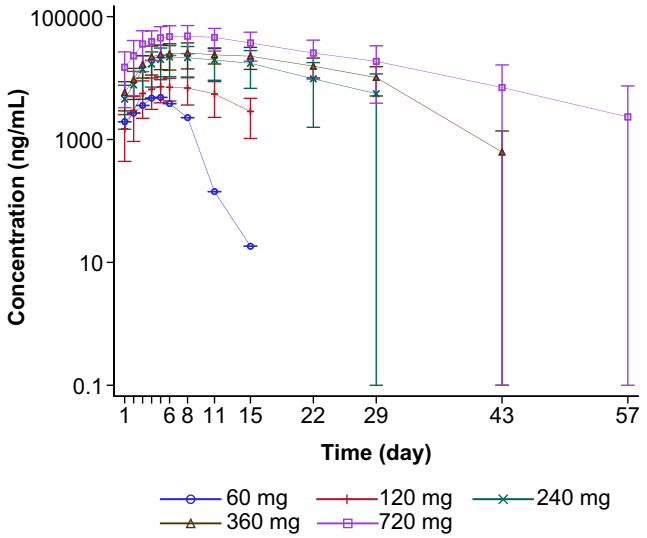

FIGURE 2 Serum SHR-1819 concentration–time profile. Data are presented as mean (standard deviation).

relationship in IgE reduction was observed across the different dosages.

ADA

The ADA analysis included 42 subjects who had at least one ADA result after being administered with either SHR-1819 or a placebo. No subject had a pre-existing ADA sample at baseline. Of the 42 subjects, 15 (35.7%) subjects who were treated with SHR-1819 had at least one treatment-induced ADA-positive sample at any time during the observation or follow-up period (Table S3). Conversely, 27 (64.3%) subjects were reported as ADA-negative. The occurrence of treatment-induced ADA positivity was reported across all cohorts treated with SHR-1819, without any discernible correlation with dosage. The earliest ADA onset was noted on Day 15, with the majority of ADA-positive cases occurring on Days 57 and 85. There was no obvious effect observed in corresponding PK profiles in most of the ADA-positive subjects.

DISCUSSION

This first-in-human study demonstrated that SHR-1819 was generally safe and well-tolerated over a dose range of 60 to 720 mg in healthy subjects. The majority of AEs were mild-to-moderate in severity. The exposure of SHR-1819 increased in a manner greater-than-proportional with a dose range of 120 to 720 mg. Administration of SHR-1819 resulted in decreases in the percentage changes of TARC/CCL17 and IgE.

The safety results demonstrated good tolerability of SHR-1819 when administered from 60 to 720 mg. All AEs recovered by the last visit of the safety follow-up. The overall incidence of AEs in the SHR-1819 treatment group was comparable to that in the placebo group. No obvious dose-dependent response was observed in severity or incidence of AE. The most frequently reported AEs in the SHR-1819 treatment groups were injection site reaction and headache, which aligns with the safety data reported for dupilumab in healthy subjects.[23] The incidences of any cause and treatment-related injection site reaction and headache in the SHR-1819 groups were not greater than those in the placebo group, further supporting the tolerability of SHR-1819. For subjects in the 240 to 720 mg dose groups who received injections at multiple sites on the abdomen, there were no significant differences in the incidences of injection site reaction compared with those in the 60 and 120 mg dose groups, in which patients received only one injection. This indicates that the frequency and severity of injection site reaction did not appear to be influenced by the number of injection sites or the higher dose levels. As this was a phase I study with a limited sample size, single administration design, and a short follow-up period, it is necessary to explore whether SHR-1819 is associated with other dupilumab-related AEs, such as hypersensitivity, conjunctivitis and keratitis, and arthralgia, in subsequent studies with a larger sample size and longer follow-up period.

The PK profile of SHR-1819, within a dose range from 60 to 720 mg, generally aligns with that of dupilumab.[23,24] After a single subcutaneous injection of SHR-1819, the median time taken to reach peak concentration is comparable to that of dupilumab, typically around 1 week. As the dose escalated from a single administration, the systemic exposure ($AUC_{0\text{-inf}}$) increased 39-fold with a 12-fold dose increase. This observation was further corroborated by power model analysis, which indicated that the total exposure (AUC) of SHR-1819 increased in a greater-than-proportional manner with dose escalation while the C_{max} exhibited dose proportionality within the dose range of 120 to 720 mg. The greater-than-proportional increase in total exposure (AUC) with increasing dose may suggest the presence of a threshold dose beyond which the exposure of SHR-1819 increases significantly, and this evidence could be valuable in optimizing the dosing regimen of SHR-1819 in subsequent studies. Furthermore, the clearance of SHR-1819 gradually decreased as the dose increased from 60 to 720 mg. This nonlinear, target-mediated clearance pathway may hint at a saturation effect at higher doses, a phenomenon also observed with other therapeutic mAbs, and further impact on drug response and the dosing strategy.

The PD results revealed that single administration of SHR-1819 resulted in a modest decrease in the

TABLE 3 Pharmacokinetics parameters of SHR-1819.

PK parameter (unit)	60 mg (*N* = 1)	120 mg (*N* = 8)	240 mg (*N* = 8)	360 mg (*N* = 8)	720 mg (*N* = 8)
T_{max} (day)	4.00 (4.00–4.00)	5.00 (3.00–10.00)	6.09 (5.00–14.23)	7.09 (3.00–14.17)	6.08 (4.00–10.19)
C_{max} (μg/mL)	4.84	6.94 (64.1)	19.6 (68.4)	25.9 (37.3)	47.1 (45.2)
$AUC_{0\text{-inf}}$ (day*μg/mL)	26.9	62.5 (103.8)	345 (104.2)	561 (39.0)	1040 (57.5)
$AUC_{0\text{-last}}$ (day*μg/mL)	26.9	66.7 (83.7)	329 (101.6)	536 (42.7)	996 (62.9)
$t_{1/2}$ (day)	1.11	2.88 (53.2)	5.12 (43.6)	5.97 (47.7)	5.51 (46.0)
V_z/F (mL)	3580	6870 (84.1)	4650 (65.2)	4920 (57.2)	5040 (80.3)
CL/F (mL/day)	2230	1920 (103.6)	696 (104.1)	641 (39.0)	693 (57.5)
MRT (day)	4.17	7.88 (20.0)	12.8 (27.3)	15.8 (13.1)	16.0 (30.5)

Note: Geomean (%CVb) for all the PK parameters except median (range) for T_{max} and mean (%CV) for $t_{1/2}$.

Abbreviations: %CV, coefficient of variation; %CVb, geometric coefficient of variation; $AUC_{0\text{-inf}}$, area under the plasma concentration–time curve from zero to infinity; $AUC_{0\text{-last}}$, area under the plasma concentration–time curve from zero to time of the last quantifiable concentration after dosing; CL/F, apparent total clearance; C_{max}, maximum plasma concentration; MRT, mean residence time; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution.

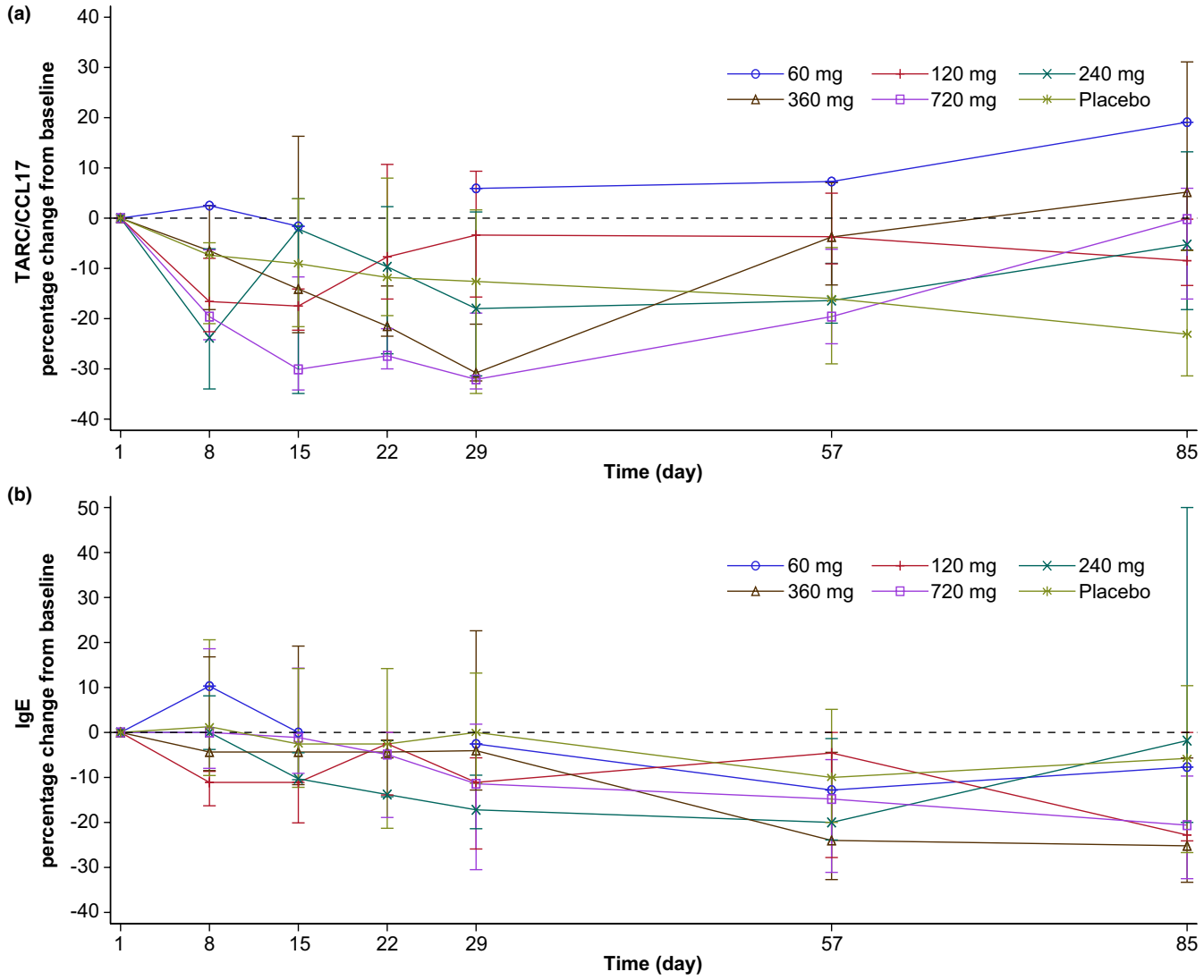

FIGURE 3 Percentage changes from baseline in concentrations of (a) TARC/CCL17 and (b) IgE over time. Data are presented as median (interquartile range).

concentrations of inflammation factors such as TARC/CCL17 and IgE, when compared with the placebo group. These data were consistent with the evidence of inhibition of the IL-4 and IL-13 signaling pathway in preclinical studies. The ability of SHR-1819 to attenuate the levels of these inflammation factors underscores the promising potential of SHR-1819 for the management of a broad spectrum of diseases characterized by heightened inflammation. Of note, the reduction in IgE levels lacks a dose–response relationship. This could be attributed to the small sample size, high variability in IgE levels among subjects, the single-dosing design, and the fact that the study was conducted on healthy participants who had lower baseline IgE levels compared with the target population. Future trials involving a larger sample size and multiple doses of SHR-1819 in the target population will provide further confirmation of the changes in IgE levels with SHR-1819 treatment. Additionally, while these preliminary results are encouraging, further investigations are required to fully elucidate the long-term anti-inflammatory activity of SHR-1819.

The primary limitation of this study was the small sample size, which may reduce the statistical power of the study and restrict the generalizability of the study findings to a broader population. Second, the study employed a single-dose design. This design limited our understanding of the safety, PK, and PD profiles of SHR-1819 over repeated exposure. Third, the short follow-up period may not be sufficient to assess the long-term safety, PK, and PD of SHR-1819, particularly if there are delayed-onset AEs or if the activity of the study drug diminishes over time. However, it is worth noting that the results of this study were preliminary and need to be validated in further studies.

In this first-in-human study, the results demonstrated that SHR-1819 was generally safe and well-tolerated within the dose range of 60 to 720 mg. The exposure of SHR-1819 increased in a greater-than-proportional manner with increasing doses from 120 to 720 mg. This indicates that the PK of SHR-1819 may not follow a linear pattern, thereby necessitating further investigation to optimize dosing regimens. Moreover, the administration of SHR-1819 resulted in decreases in the concentrations of inflammatory biomarkers TARC/CCL17 and IgE, which suggests the therapeutic potential of SHR-1819 in treating type 2 inflammatory diseases.

AUTHOR CONTRIBUTIONS

N.L. and K.S. wrote the manuscript. N.L., S.S., and K.S. designed the research. S.S., N.L., W.Q., X.Y., P.L., T.K.N., X.B., and K.S. performed the research. W.Q. and T.K.N. analyzed the data.

ACKNOWLEDGMENTS

We thank all the participants and their families for participating in this trial, and all investigators and site personnel. Medical writing support was provided by Tengfei Zhang (Hengrui) according to the Good Publication Practice Guidelines.

FUNDING INFORMATION

The study was sponsored by Atridia and Jiangsu Hengrui Pharmaceuticals Co., Ltd.

CONFLICT OF INTEREST STATEMENT

N.L., W.Q., T.K.N., X.Y., P.L., X.B., and K.S. are employees of Jiangsu Hengrui Pharmaceuticals Co., Ltd. All other authors declared no competing interests for this work.

ORCID

Na Li https://orcid.org/0009-0001-9511-2384
Sepehr Shakib https://orcid.org/0000-0002-7199-5733
Weilin Qian https://orcid.org/0009-0005-9851-6869
Xiaoyan Yao https://orcid.org/0009-0008-8278-6241
Puyuan Li https://orcid.org/0009-0006-3610-2617
Tsz Keung Nip https://orcid.org/0009-0001-6052-5111
Xiaoyan Bai https://orcid.org/0009-0008-5358-0594
Kai Shen https://orcid.org/0009-0009-0439-635X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Li N, Shakib S, Qian W, et al. Safety, pharmacokinetics, and pharmacodynamics of anti-IL-4Rα antibody SHR-1819 in healthy subjects: A randomized, controlled phase I study. *Clin Transl Sci*. 2024;17:e13763. doi:10.1111/cts.13763