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Safety, tolerability, pharmacokinetics, immunogenicity, and pharmacodynamics of MG-ZG122, a long-acting humanized anti-thymic stromal lymphopoietin mAb, in healthy Chinese: a randomized, double-blind, placebo-controlled, dose-escalation, phase I study

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ORIGINAL RESEARCH

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Safety, tolerability, pharmacokinetics, immunogenicity, and pharmacodynamics of MG-ZG122, a long-acting humanized anti-thymic stromal lymphopoietin mAb, in healthy Chinese: a randomized, double-blind, placebo-controlled, dose-escalation, phase I study

Xuan Zhang[a*], Lingqiao Zhu[b*], Qian Zhang[a], Liang Zheng[a], Jinlin Guo[b], Qiuling Zou[b], Rui Yan[b], Di Qin[c], Chenghai Zhang[b] and Wei Hu[a]

[a]Department of Clinical Pharmacology, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China; [b]R&D Department, Shanghai Mabgeek Therapeutics Co., Ltd., Shanghai, China; [c]Medical Management Department, Shanghai Mabgeek Therapeutics Co, Ltd, Shanghai, China

ABSTRACT

Background: This phase I study aimed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of MG-ZG122, an anti-thymic stromal lymphopoietin mAb, in a healthy Chinese population.

Methods: A randomized, double-blind, placebo-controlled, and dose-escalation design was used. Four dose cohorts (52.5, 105, 210, and 420 mg) with 10 participants each were randomized to receive subcutaneously (SC) a single dose of MG-ZG122 or placebo (8:2), except for the 52.5 mg with 4 participants (2:2).

Results: Among participants who received MG-ZG122 ($n = 26/34$), most treatment-emergent adverse events (TEAEs) were grade 1 or 2. A single dose of MG-ZG122 exhibited a dose-dependent increase in the serum concentration ranging from 52.5 to 420 mg. It showed a half-life of up to 80 days and is intended to support a once-every-6-month administration. Dose-dependent reductions in peripheral blood eosinophil counts were observed in the 210 and 420 mg dose cohorts, with a greater decrease at the 420 mg and a sustained response through day 211.

Conclusions: MG-ZG122 was safe and well-tolerated with favorable PK profiles after a single SC injection in healthy Chinese at doses ranging from 52.5 to 420 mg, providing preliminary evidence for further evaluation.

Clinical trial registration: This study was registered with ClinicalTrials.gov, NCT05659927.

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KEYWORDS
MG-ZG122; thymic stromal lymphopoietin; asthma; safety; monoclonal antibody; pharmacokinetics

1. Introduction

Asthma, as a common airway inflammatory respiratory disease, affects up to 300 million people of all ages around the world [1], and the number of people aged 20 years old and above with asthma in China is 45.7 million [2]. Many different fixed-dose combinations of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABAs) have been recommended for maintenance or reliving therapy in patients with mild to moderate, or even severe asthma [3–5]. However, there are still some patients with poor control due to the heterogeneity of airway inflammation, severe airway remodeling, genetic factors, and decreased glucocorticoid responsiveness [6–8]. This patient population is associated with reduced quality of life, frequent use of oral corticosteroids, and increased healthcare resource utilization.

The heterogeneity of asthma in pathogenesis, disease progression, and response to treatment is one of the critical obstacles to its management and drug development [8,9]. Type 2 airway inflammation, which dominates the majority of patients with asthma, is driven by cytokines-mediated [interleukin (IL)-4, IL-5, and IL-13] inflammatory cascade produced by type 2 T-helper (Th2) cells and type 2 innate lymphoid cells (ILC2) [10,11]. Fractional exhaled nitric oxide (FeNO) and blood eosinophil (EOS) count are produced through the action of cytokine mediators. Biologics involving specific downstream cytokines of type 2 inflammation [10,12], such as omalizumab (anti-immunoglobulin E/IgE), reslizumab (anti-IL5), mepolizumab (anti-IL5), benralizumab (anti-IL-5 R), and dupilumab (anti-IL-4 Rα), are approved and recommended by guidelines as the add-on treatment for severe Th2 asthma [3,5], though their use is restricted to specific populations-omalizumab requires defined serum IgE levels, while IL-5/IL-5 R-targeted agents depend on elevated eosinophil counts. However, as a novel therapeutic target, thymic stromal lymphopoietin (TSLP) can not only promote Th2-type inflammation but also has evidence to support its role in initiating non-Th2-type inflammatory processes in asthma [13,14]. As an epithelial-derived cytokine, TSLP activates JAK and STAT5 signaling pathways by binding to its receptor (TSLPR) and interleukin-7 receptor α (IL-7 Rα) in a high-affinity heterodimeric

CONTACT Chenghai Zhang chenghai.zhang@mabgeek.com R&D Department, Shanghai Mabgeek Therapeutics Co., Ltd., Building 5, No. 34, Lane 122, Chunxiao Road, Zhangjiang Hi-Tech Park, Pudong New Area, Shanghai 200120, China; Wei Hu drweihu@163.com Department of Clinical Pharmacology, The Second Affiliated Hospital of Anhui Medical University, No. 678, furong Road, Economic and Development District, Hefei, Anhui 230601, China
*These authors have contributed equally to this work and share first authorship.

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complex [15,16]. It is released following pro-inflammatory stimuli and drives allergic and non-allergic inflammatory responses through activating multiple inflammatory cells, such as dendritic cells (DCs), ILC2s, mast cells, and other immune cells [13,17]. Currently, tezepelumab (TEZSPIRE™), a human immunoglobulin G2λ (IgG2λ) monoclonal antibody (mAb) that inhibits the action of TSLP, is the only biologic approved as an add-on maintenance treatment for severe asthma, with no restrictions based on phenotype or biomarkers [18]. Notably, although it was approved for marketing by the US FDA as early as 2021, with the recommended dosage being a 210 mg subcutaneous injection every 4 weeks, tezepelumab has not yet been launched in China. Consequently, there exists an unmet medical need among such patient population in China.

MG-ZG122, a humanized anti-TSLP mAb (IgG1) developed by Hunan Mabgeek Biotech Co., Ltd., was engineered with structural mutations to extend its half-life. As an Fc-modified antibody, it exhibits high affinity for FcRn, a feature that contributes to its prolonged half-life. This optimized pharmacokinetic profile may enable MG-ZG122 to support a dosing interval of once every 6 months. In contrast to tezepelumab, which requires administration every 4 weeks, this extended dosing schedule is expected to improve patient compliance and convenience. Preclinical studies revealed that MG-ZG122 inhibits the activation of its downstream signaling pathways and reduces the inflammatory response in vitro and in vivo by effectively blocking the binding of TSLP to its receptor complex, that it could be a promising drug candidate for asthma or chronic obstructive pulmonary disease (COPD) (internal unpublished data). Here, we report the results from a first-in-human, dose-escalation phase I study. The aim of the study was to determine the safety, tolerability, pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of a single dose of MG-ZG122 in healthy adult subjects.

2. Methods

2.1. Study design

This randomized, double-blind, placebo-controlled, dose-escalation, phase I study (Clinicaltrials.gov identifier: NCT05659927) was designed to evaluate the safety, tolerability, PKs, immunogenicity, and PDs of MG-ZG122 in healthy adult participants. The study was conducted from 9 February 2023, to 3 January 2024, at a single site, the Second Hospital of Anhui Medical University, in China. This single-ascending-dose (SAD) study included four planned dose cohorts (52.5, 105, 210, and 420 mg), with 10 participants (8:2) in each randomized to receive subcutaneously a single dose of MG-ZG122 or placebo, except for the 52.5 mg cohort of 4 participants (MG-ZG122 vs. placebo = 2:2).

This study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) for Good Clinical Practice (GCP), and appropriate local regulatory requirements. The study protocol, informed consent form, and related amendments were approved by the Ethics Committee at the study site [YW2022-103 (F1)]. Written informed consent was obtained from each subject before study entry.

2.2. Study participants

Healthy adult volunteers aged 18–65 years (inclusive), with body weight ≥50 kg for males and ≥40 kg for females, and a body mass index (BMI) in a range of 19 and 26 kg/m^2 (inclusive) were eligible for this study. Eligible participants were deemed in good health with no clinically significant findings through medical history screening, physical examination, vital sign measurements, laboratory tests, electrocardiogram (ECG), chest radiography, etc. Participants were excluded if they: (1) had a history or current presence of diseases, including malignancy, tuberculosis, neurologic, respiratory, cardiovascular and cerebrovascular, gastrointestinal, hematologic, urinary, endocrine, and immune diseases; (2) had acute or subacute infections within 2 weeks before screening, or acute or chronic infections history within 4 weeks before screening, and received systemic anti-infective treatment; (3) known allergic reactions to any monoclonal antibody, MG-ZG122 and/or any of its excipients; (4) had any surgical interventions and vaccinations that might interfere with the study within 4 weeks before screening, or planned to do during the study; (5) had received any biological agents or non-biological agents within 3 months or 5 half-lives of any drugs before screening (whichever is longer); (6) had received any prescription medications within 2 weeks, or non-prescription drugs or Chinese herbal drugs within 1 week before the first dose. Full eligibility criteria are presented in Supplementary Table S1.

2.3. Study procedures

Four participants in the 52.5 mg dose cohort were randomly assigned in a 1:1 ratio (n = 2:2) to receive either MG-ZG122 or placebo via subcutaneous on Day 1 of the study, and 10 participants in each of the latter three dose levels (105, 210, and 420 mg) were randomized in an 8:2 ratio (MG-ZG122 vs. placebo = 8:2). The dose escalation decision was made based on a review of safety data up to Day 12 of the current cohort by the investigator and sponsor. Participants in the dose level of 52.5 mg were discharged and to be followed from Day 8 to Day 127, whereas those in the other dose cohorts (105, 210, or 420 mg) were followed up to Day 155, and additional follow-up assessments to Days 211 and 239 were then performed at the discretion of the investigator and the sponsor.

2.4. Randomization and masking

The entire randomization process was conducted independently by the clinical research organization (CRO). Blocked randomization was used, and the sequences was generated by unblinded CRO's biostatisticians using SAS (version 9.4) (SAS Institute Inc., Cary, NC). Specifically, unblinded biostatisticians were solely responsible for generating the randomization schedule, managing the blinding and labeling. These personnel had no communication with the investigators or study staffs regarding the treatment assignments and did not disclose the blinding details to them to ensure eliminate potential bias. Eligible participants were assigned random numbers in ascending order of their screening numbers. Simple random sampling was performed by the unblinded biostatisticians to allocate investigational products. The placebo, which is an excipient without the active

ingredient MG-ZG122, was indistinguishable from MG-ZG122 in appearance, color, and shape. Participants and investigators (including sponsors) were blinded to the treatment assignments throughout the study.

2.5. Safety and tolerability assessments

Theprimaryendpoint was to determine the safety and tolerability of MG-ZG122.Given the single-dose design of the study, tolerability was assessed by predefined termination criteria based on Common Terminology Criteria for Adverse Events (CTCAE) V5.0: dose escalation terminates if > 50% (≥1/2) of participants in a dose cohort experience Grade ≥2 treatment-related adverse events (TRAEs), > 33% (≥1/3) have Grade ≥3 TRAEs, or any participant has a treatment-related serious adverse event (SAE), with a multidisciplinary team then reviewing to decide dose-ascending continuation. Safety was assessed by monitoring adverse events (AEs) and SAEs, as well as vital signs, physical examination, clinical laboratory tests (Table S5), ECG, etc. AEs and treatment-emergent adverse events (TEAEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 26.1).

2.6. Pharmacokinetics, immunogenicity, and pharmacodynamic assessment

The secondary endpoints included the PK, immunogenicity, and PD assays of MG-ZG122. Blood samples (3 mL) were collected at 1 hour (h) before dosing, 6, 12 h after dosing, and on Days 2, 3, 4, 5, 6, 8, 12, 22, 43, 71, 99, 127 (only up to this time point in 52.5 mg dose level), 155, 183, 211, and 239. The serum concentration of MG-ZG122 was detected by enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification of 100 ng/mL. The main PK parameters, including maximum observed blood drug concentration (C_{max}), time to maximum observed concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), the area under the blood concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{0-t}), AUC from time zero to infinity (AUC_{0-inf}), apparent clearance (CL/F, where F is the bioavailability), apparent volume of distribution (Vz/F), and percentage of AUC from time zero to infinity (%AUC_{ex}), and terminal elimination rate constant (λz) were calculated.

The incidence of anti-drug antibodies (ADA) was evaluated for immunogenicity assessment. Blood samples (5 mL) were collected from all participants at 1 h before dosing, and on Days 12, 43, 99, 127 (only up to this time point in the 52.5 mg dose level), 183, 211, and 239 after dosing. The anti-MG-ZG122 antibodies in blood samples were detected by electrochemiluminescence immunoassay (ECLIA). Confirmed ADA-positive samples were further analyzed for neutralizing antibodies (NAbs) using ECLIA.

The effect of MG-ZG122 on PD biomarkers was evaluated by detecting the blood levels of interleukin-5 (IL-5), Immunoglobulin E (IgE), and blood eosinophil counts (EOS). Blood samples (3 mL) for IL-5 and IgE assays were taken at 1 h before dosing, and on Days 8, 12, 22, 43, 71, 99, 127 (only up to this time point in 52.5 mg dose level), 155, 183, 211, and 239 after dosing. EOS counts were from the hematology data. Serum samples were assayed using the ECLIA for the measurement of total IgE with a commercial kit (Roche), and IL-5 was quantified using automated platforms (Ella™ & Simple Plex) with a commercial ELISA kit (ProteinSimple) according to the manufacturer's instructions.

2.7. Statistical analysis

All eligible randomized participants who received the investigational treatment (MG-ZG122 or placebo) were included in the full analysis set (FAS). The safety and tolerability analysis was based on the safety analysis set (SS), which included all randomized participants who received the MG-ZG122 or placebo and had safety data records after treatment. PK profiles were analyzed in all randomized participants, who received the investigational treatment (MG-ZG122 or placebo) and had at least one evaluable PK parameter or concentration data. The immunogenicity analysis was performed in the immunogenicity analysis set (IAS), defined as all randomized participants who received the investigational treatment (MG-ZG122 or placebo) and had at least one data post-baseline for immunogenicity evaluation.

All statistical analyses were conducted using SAS (version 9.4) (SAS Institute Inc., Cary, NC). For demographics, continuous variables were presented as mean ± standard deviation SD) or median (interquartile range/IQR); categorical data were expressed using frequency and percentage. The safety data, PK parameters, ADA results, and PD biomarkers were analyzed using descriptive statistics and summarized by dose cohorts. For PK analysis, PK parameters for MG-ZG122 were calculated using a non-compartmental model by WinNonlin 8.3.1 (Certara, Inc), and PK parameters (C_{max}, AUC) were log-transformed to linearize relationships and stabilize variance. A power model ($\log(y)=\beta_0+\beta_1\cdot\log(\text{dose})$) was applied using mixed-effects modeling (with log(dose) as a fixed effect) to assess dose proportionality across 52.5–420 mg, with proportionality confirmed if the 90% confidence interval (CI) of β_1 included 1. Missing PK concentrations or parameters were not imputed, excluded from summaries but retained in listings as 'NC' for transparency.

3. Results

3.1. Participants' disposition and baseline characteristics

Between February 2023 and January 2024, 125 healthy volunteers were screened, among whom 36 participants were enrolled and randomly assigned to the treatment groups, and 2 participants dropped out before administration. The number of participants ($n = 34$) in the dosing cohorts was as follows: 2 participants in 52.5 mg of MG-ZG122, 8 in 105 mg, 8 in 210 mg, 8 in 420 mg, and 8 cases in the placebo group. Finally, 31 out of 34 participants completed the study and 3 withdrew from the study (Figure 1).

The detailed demographics and baseline characteristics of the MG-ZG122 and placebo groups are shown in Table 1. Of the 34 randomized participants, 26 received different doses of MG-ZG122, and 8 received placebo, with an overall mean ±SD

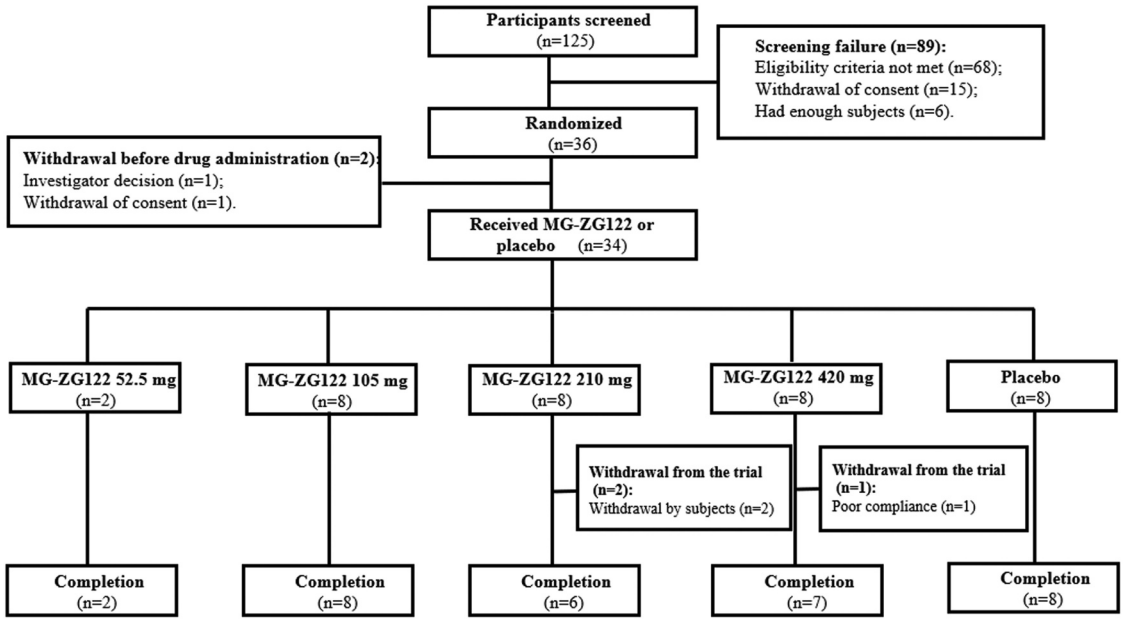

Figure 1. Study participants' disposition.

Table 1. Summary of subject demographics and baseline characteristics (full analysis set, fas).

	MG-ZG122					
Characteristics	52.5 mg (n = 2)	105 mg (*n* = 8)	210 mg (*n* = 8)	420 mg (*n* = 8)	Total (*n* = 26)	Placebo (n = 8)
Age (year), [Mean±SD]	22.5 ± 6.36	33.5 ± 7.29	30.1 ± 4.58	26.6 ± 6.25	29.5 ± 6.72	31.6 ± 8.83
Sex, [n(%)]						
Male	2 (100.0)	6 (75.0)	6 (75.0)	7 (87.5)	21 (80.7)	6 (75.0)
Female	0	2 (25.0)	2 (25.0)	1 (12.5)	5 (19.2)	2 (25.0)
Ethnicity, [n(%)]						
Han	2 (100)	8 (100)	8 (100)	8 (100)	26 (100)	8 (100)
Others	0	0	0	0	0	0
Height (cm), [Mean±SD]	170.8 ± 4.60	170.2 ± 9.20	170.7 ± 8.48	171.2 ± 5.75	170.7 ± 7.35	168.3 ± 10.97
Weight (kg), [Mean±SD]	72.9 ± 8.20	63.1 ± 4.35	67.4 ± 9.93	68.8 ± 7.64	66.9 ± 7.79	62.2 ± 10.47
Smoking history, [n(%)]						
Yes	0	0	0	0	0	0
No	2 (100)	8 (100)	8 (100)	8 (100)	26 (100)	8 (100)
BMI (kg/m2), [Mean±SD]	24.95 ± 1.49	21.86 ± 1.71	23.03 ± 1.84	23.44 ± 2.10	22.94 ± 1.97	21.88 ± 1.92
Concomitant Medications [n(%)]	0	1 (12.5)	1 (12.5)	1 (12.5)	3 (11.5)	1 (12.5)

SD: standard deviation.
BMI: body mass index, = Weight (kg)/Height^2 (m^2).

age of 29.5 ± 6.72 and 31.6 ± 8.83 years, respectively. Most participants in both groups were men (MG-ZG122 vs. placebo: 80.7% and 75.0%). Mean BMI across the groups ranged from 21.88 ± 1.91 to 22.94 ± 1.97 kg/m^2. All the enrolled participants (*n* = 34) had no prior medications, and 4 (4/34, 11.8%) took at least one concomitant medication, but their drug use was considered to have no impact on the study.

3.2. Safety and tolerability

A total of 34 participants received an injection and were analyzed in the SS with 26 in the MG-ZG122 group and 8 in the placebo group. A summary of AEs in the SAD study is presented in Table 2. Overall, 57 TEAEs were reported in 20 (*n* = 20/26, 76.9%) and 5 (*n* = 5/8, 62.5%) participants in the MG-ZG122 and placebo groups, respectively. A total of 17 participants (17/34, 50%) experienced 30 treatment-related adverse events (TRAEs), of which 14 were MG-ZG122 related (*n* = 14/26, 53.9%) and 3 were placebo related (*n* = 3/8, 37.5%). Only one case (*n* = 1/8, 12.5%) of Grade ≥3 TEAEs occurred in the placebo group, which resulted from splenic rupture due to fall from a horse. No TEAEs led to study withdrawal or death during the study. The most common TEAEs (≥10% of participants) in the MG-ZG122 group (*n* = 26) were urinary protein presence (26.9%), blood uric acid elevated (15.4%), white blood cell counts increased (11.5%), and blood triglyceride increased (11.5%). TEAEs that occurred more frequently in the placebo group (*n* = 8) were upper respiratory tract infection (25.0%), urinary protein presence, blood bilirubin increased, elevated unconjugated bilirubin, elevated blood fibrinogen, elevated platelet count, fracture, splenic rupture, neurotrauma, oral ulcer, pelvic effusion was all 12.5%.

3.3. PK results

Twenty-six subjects treated with MG-ZG122 were finally included in PK analyses. As shown in the serum concentration-

Table 2. Summary of incidence of treatment-emergent adverse events (TEAEs) (safety analysis set, ss).

	MG-ZG122					
	52.5 mg (n = 2)	105 mg (*n* = 8)	210 mg (*n* = 8)	420 mg (*n* = 8)	Total (*n* = 26)	Placebo (n = 8)
Treatment-emergent adverse events (TEAEs), n (%)	2 (100)	3 (37.5)	8 (100)	7 (87.5)	20 (76.9)	5 (62.5)
Treatment-related adverse events (TRAEs), n (%)	2 (100)	3 (37.5)	5 (62.5)	4 (50.0)	14 (53.9)	3 (37.5)
Serious adverse events (SAEs), n (%)	0	0	0	0	0	1 (12.5)
Treatment-related SAEs (TRSAEs), n (%)	0	0	0	0	0	0
Grade ≥3 TEAEs, n (%)	0	0	0	0	0	1 (12.5)
Grade ≥3 TRAEs, n (%)	0	0	0	0	0	0
TEAEs, > 10% of the total subjects in the MG-ZG122 or placebo groups, n (%)						
Urinary protein presence	2 (100)	1 (12.5)	2 (25)	2 (25)	7 (26.9)	1 (12.5)
Blood uric acid elevated	0	0	1 (12.5)	3 (37.5)	4 (15.4)	0
White blood cell count increased	0	0	1 (12.5)	2 (25)	3 (11.5)	0
Blood triglyceride increased	0	0	2 (25)	1 (12.5)	3 (11.5)	0
Blood bilirubin increased	0	0	1 (12.5)	0	1 (3.8)	1 (12.5)
Unconjugated bilirubin increased	0	0	1 (12.5)	0	1 (3.8)	1 (12.5)
Blood fibrinogen increased	0	0	0	0	0	1 (12.5)
Elevated platelet count	0	0	0	0	0	1 (12.5)
Upper respiratory tract infection	0	0	1 (12.5)	1 (12.5)	2 (7.7)	2 (25.0)
Fracture	0	0	0	0	0	1 (12.5)
Splenic rupture	0	0	0	0	0	1 (12.5)
Neurotrauma	0	0	0	0	0	1 (12.5)
Oral ulcer	0	1 (12.5)	0	0	1 (3.8)	1 (12.5)
Pelvic effusion	0	0	0	0	0	1 (12.5)
TRAEs, > 5% of the total subjects in the MG-ZG122 or placebo groups, n (%)						
Urinary protein presence	2 (100)	1 (12.5)	2 (25)	2 (25)	7 (26.9)	1 (12.5)
Urinary red Blood cells positive	1 (50)	0	1 (12.5)	0	2 (7.7)	0
Occult blood in urine positive	0	0	2 (25)	0	2 (7.7)	0
Blood fibrinogen decreased	0	2 (25)	0	0	2 (7.7)	0
Blood bilirubin increased	0	0	1 (12.5)	0	1 (3.8)	1 (12.5)
Unconjugated bilirubin increased	0	0	1 (12.5)	0	1 (3.8)	1 (12.5)
Blood fibrinogen increased	0	0	0	0	0	1 (12.5)
Oral ulcer	0	1 (12.5)	0	0	1 (3.8)	1 (12.5)

TEAEs: treatment-emergent adverse events.
TRAEs: treatment-related adverse events.

time curves (Figure 2), the mean serum concentration of MG-ZG122 in healthy participants increased with doses ranging from 52.5 mg to 420 mg, and the trend of serum concentration changes over time was similar in all dose cohorts. The main PK parameters of MG-ZG122 are summarized by dose level in Table 3. The median T_{max} after a single SC dose ranged from 5 to 21 Days. The mean C_{max} increased with increasing dose of MG-ZG122 from 5.5 to 35.1 μg/mL. The mean half-life ($t_{1/2}$) after a single SC dose ranged from 49.8 to 81.5 Days across dose cohorts. Both $AUC_{0\text{-}t}$ (430.2–3393.7 day.μg/mL) and $AUC_{0\text{-}inf}$ (1034.7–3955.8 day.μg/mL) increased with escalating doses from 52.5 mg to 420 mg. The geometric mean clearance (CL) was similar among the four treatment cohorts.

Moreover, a power model method was used to evaluate the dose proportionality based on the PK parameters including C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$. With the dose ranging from 52.5 mg to 420 mg, the slope estimates of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ were 0.904 (90% confidence interval/CI: 0.774, 1.035), 0.933 (90% CI: 0.807, 1.060), and 0.978 (90% CI: 0.829, 1.127), respectively. The exposure parameters were considered to increase in an approximately proportional manner as the dose increased (Supplementary Table S2).

3.4. Immunogenicity results

Thirty-three participants (25 in the MG-ZG122 group and 8 in the placebo group) were included in the immunogenicity analysis. None of the participants were positive for ADA at baseline. Three participants (105 mg: 2 and 420 mg: 1), all from the MG-ZG122 group, tested positive for ADA after single-dose administration, corresponding to an overall positivity rate of 9.1% (3/33).Nab was negative in all 33 participants (Supplementary Table S3 and Table S4). The serum concentration exposure levels were comparable between the subjects ADA-positive and ADA-negative (Supplementary Figure S1).

3.5. PD results

Thirty-three participants were included in the PD analysis. The trend of the mean change from baseline in the biomarker EOS counts over time is shown in Supplementary Figure S2. Blood EOS counts decreased at all visits after treatment with 210 mg and 420 mg of MG-ZG22, with consistent trends in the two dose cohorts. In addition, the 420 mg dose cohort indicated a greater reduction in blood EOS levels and sustained response to Day 211. No significant dose-dependent manner was observed in the changes of blood IL-5 and IgE levels from baseline in each dose cohort after a single dose of MG-ZG22.

4. Discussion

This phase I, ascending-dose study shows the preliminary safety experience in humans and the single-dose pharmacokinetic profiles for MG-ZG122, a long-acting humanized anti-TSLP mAb with evidence of therapeutic potential for asthma and other inflammatory diseases.

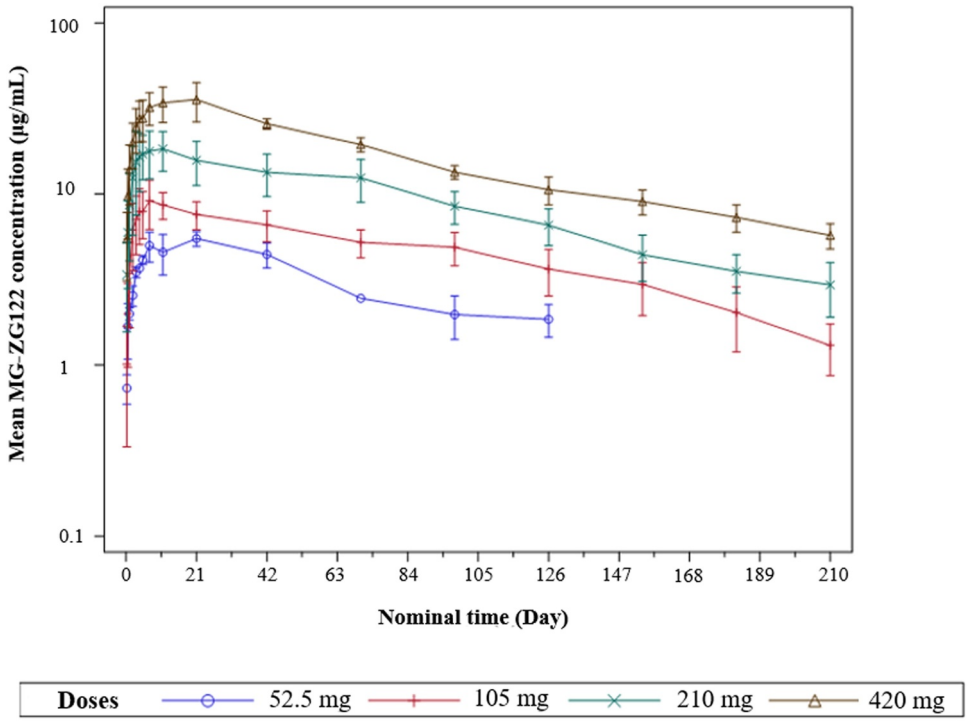

Figure 2. Semi-log scale (pk concentration analysis set, PKCS): mean (± standard deviation [sd]) blood MG-ZG122 concentration-time profiles in healthy participants following single-dose at 52.5, 105, 210, and 420 mg.

Table 3. Summary of pharmacokinetic parameters of MG-ZG122 after a single-dose subcutaneous injection (pk parameter analysis set, PKPS).

	MG-ZG122			
Variables	52.5 mg (N = 2)	105 mg (*N* = 8)	210 mg (*N* = 8)	420 mg (*N* = 8)
T_{max} (day)				
n	2	8	8	8
Median (Min, Max)	21.0 (21, 21)	7.0 (4, 11)	5.0 (3, 11)	16.0 (4, 21)
C_{max} (μg/mL)				
n	2	8	8	8
Geometric mean (%CV)	5.5 (9.83)	9.5 (24.91)	19.0 (30.09)	34.0 (27.46)
$t_{1/2}$ (day)				
n	2	7	7	7
Geometric mean (%CV)	61.7 (1.95)	49.2 (17.50)	70.1 (10.30)	80.4 (17.33)
AUC_{0-t} (day·μg/mL)				
n	2	8	6	7
Geometric mean (%CV)	425.2 (22.00)	923.9 (20.95)	1779.5 (25.59)	3367.2 (13.80)
AUC_{0-inf} (day·μg/mL)				
n	0	7	6	6
Geometric mean (%CV)	N/A	1012.2 (22.82)	2072.0 (26.94)	3920.1 (15.20)
CL/F (L/day)				
n	0	7	6	6
Geometric mean (%CV)	N/A	0.1 (22.82)	0.1 (26.94)	0.1 (15.20)
Vz/F (L)				
n	0	7	6	6
Geometric mean (%CV)	N/A	7.4 (32.06)	10.4 (23.25)	11.9 (14.92)
$\%AUC_{ex}$ (%)				
n	2	8	8	7
Geometric mean (%CV)	27.7 (1.52)	9.2 (38.98)	19.0 (69.90)	16.3 (20.86)

Data were expressed as geometric mean (%CV) except for T_{max}, which was described as median (minimum, maximum).
T_{max}: time to maximumserum concentration; C_{max}: peak serumconcentration; $t_{1/2}$: terminal elimination half-life; AUC_{0-t}: area under the serum concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-inf}: area under the serum concentration-time curve from time zero to infinity; CL: clearance; $\%AUC_{ex}$: percentage of area under the concentration-time curve from time zero to infinity; λz: terminal elimination rate constant.

In this study, a single-dose injection of MG-ZG122 was safe and well-tolerated in all four dose cohorts from 52.5 to 420 mg. The percentage of participants who experienced TEAEs was comparable between the MG-ZG122 (76.9%) and placebo (62.5%) groups. No SAEs, deaths, or withdrawals due to TEAEs related to MG-ZG122 were reported in any participants. All drug-related TEAEs were grade 1 or 2. No dose dependence was observed for either TEAE or TRAEs. This is similar to the

safety results of a phase 1 study of Tezepelumab in healthy populations, with a TEAE rate of 60% (vs. placebo 69%) after a single dose, and no deaths and SAEs reported [19]. In a phase 2b study of tezepelumab in adults with uncontrolled moderate-to-severe asthma, at least one TEAE was reported in 65.9% of the patients in the placebo group and 66.0% of those in the tezepelumab group, with the majority of TEAEs (71%) being mild or moderate in severity [20]. In a phase 1 study of SHR-1905, another humanized anti-TSLP monoclonal antibody, the TEAE rates were 82.5% and 60.0%, respectively, as compared with placebo. No SAEs or deaths occurred during the study [21]. The most common TEAEs were urinary protein presence, elevated blood uric acid, elevated white blood cell count, and elevated blood triglyceride. These laboratory abnormalities were classified as transient because each of the abnormal measures was confirmed to be isolated (only one abnormal value was recorded on laboratory testing) and had returned to the normal reference range by the time of the next scheduled study visit. All the clinically observed abnormalities were transient and resolved without intervention. In addition, no evidence of nephrotoxicity or renal damage was observed in our preclinical studies (data have not yet been published). Therefore, taken together the investigator's consideration, we speculate that these laboratory changes may be related to physiological factors in normal circumstances, such as short-term exercise or dietary changes, rather than to treatment-related toxic effects.

MG-ZG122 fits the PK characteristics of an antibody-drug, with a long half-life in vivo. There is no evidence of target-mediated clearance in the dose range studied. After a single-dose SC injection of MG-ZG122 ranging from 105 to 420 mg, the PK parameters, including C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ increased in a linearly proportional manner as the dose increased. The median time to maximum blood concentration (T_{max}) ranged from 5 to 21 Days. This is similar to the linear PK profile of currently marketed biologic tezepelumab, which has a T_{max} ranging from 81 to 237 hours (3 to 10 days) after a single SC dose [19]. A slight trend of half-life ($t_{1/2}$) prolongation (49.8 to 81.5 days) with increasing doses ranging from 105 to 420 mg was observed. Notably, the half-life ($t_{1/2}$) of MG-ZG122 at 210 and 420 mg doses (70.4 to 81.5 Days) was approximately 2.7 to 3.5 times as high as those of equivalent Tezepelumab [19]. For the 52.5 mg dose cohort, the observed $t_1/_2$ was 51.2 days; however, with only 2 participants in this cohort, we cannot rule out the potential influence of the small sample size on the observed trend. As an IgG1κ antibody with an Fc-modified domain, MG-ZG122 exhibits an extended half-life, a feature that may contribute to these pharmacokinetic characteristics [22]. In future studies, we plan to further explore the potential impact of population PK to provide more comprehensive insights. The long half-life of MG-ZG122 enables a potential administration interval of 6 months or longer, directly reducing the number of drug administrations and alleviating dose burden. This extended dosing interval is expected to lower financial burden by decreasing the number of drug units required and reducing hospital visit frequency, such as transportation expenses and work absences [23,24].

Three ADA-positive cases (11.5%) were observed in participants receiving different doses of MG-ZG122, and all of them are Nab negative, indicating that the incidence of immunogenicity of MG-ZG122 in Chinese healthy adult participants is low after a single dose. ADA positivity had no significant effect on the exposure concentration of MG-ZG122.

Given the heterogeneity of asthma, predictive biomarker identification offers an opportunity for phenotype-specific interventions and the realization of personalized treatment. The role of EOS in asthma inflammation is well known as they mediate asthma development and airway remodeling [25]. The guidelines [3,5] also indicate that peripheral blood eosinophil count can be used as an indicator to evaluate the type of airway inflammation and the level of asthma control. Both allergic and eosinophilic asthma are mechanistically driven by type 2 inflammation, and elevated eosinophil counts are a common feature [26]. In addition to the inflammatory cytokine IL-5 involved in Th2 asthma that promotes EOS recruitment and activation, other auxiliary drivers of the T2 inflammatory cascade promote B-cell class switching and immunoglobulin type E (IgE) production [10,27]. After a single subcutaneous injection of MG-ZG122, there was no significant dose-dependent trend in the changes of IL-5 and IgE from baseline in all dose cohorts. The results were similar to those of the phase I trial of the same target drug Tezepelumab (700 mg, Q4W, intravenously administered in three doses) in patients with mild asthma [28], and the effects were not significant or could not be evaluated quantitatively. We speculate that this lack of significant changes in our study may be attributed to two factors. First, this phase I study was conducted in healthy subjects, who normally have lower IgE and IL-5 levels than patients with asthma [29,30]. Second, the small sample size in each cohort, combined with the inherent variability of these biomarkers, may have limited the power to detect potential dose-dependent changes. However, as compared with placebo, MG-ZG122 reduced peripheral blood eosinophil counts in a dose-dependent manner across doses ranging from 210 mg to 420 mg, with a sustained response up to Day 211. This also suggests that MG-ZG122 has a promising therapeutic potential for asthma.

Non-type 2 (non-T2) asthma may also be driven by structural abnormalities involving airway smooth muscle as well as irregular neuronal activation [31]. Tezepelumab, an marketed antibody that neutralizes TSLP activity, significantly reduces airway inflammation and even exacerbations in patients with low blood eosinophil counts, which suggests that blockade of TSLP may provide benefits in asthma management beyond reducing T2 inflammation. Tezepelumab, as a first-in-class anti-TSLP mAb recommended at 210 mg every 4 weeks, remains unapproved in China currently [18]. MG-ZG122, a domestically developed humanized anti-TSLP mAb (IgG1), specifically binds human TSLP with high affinity to block its interaction with the TSLPR-IL7Rα complex, thereby inhibiting downstream signaling and reducing inflammatory responses. Engineered with Fc mutations to enhance FcRn binding (prolonging half-life by reducing intracellular degradation) and high-throughput screening for favorable potency, stability, and high bioavailability after subcutaneous

injection. MG-ZG122 enables potential dosing intervals of 6 months or longer. MG-ZG122 was associated with lower direct treatment costs than Tezepelumab by reducing the frequency of dosing and the number of drugs associated with it [32,33]. Compared to approved asthma biologics such as anti-IgE and anti-IL-5 pathway antibodies, anti-TSLP antibodies have demonstrated a significantly expanded patient population in clinical studies, and are expected to be an effective and safe treatment option for non-Th2 type asthma [15].

Potential limitations of this study are that all participants were healthy volunteers with a small sample size, thus limiting the insight into the drug's effects in those with asthma. Especially results from the 52.5 mg cohort require cautious interpretation due to its small size. Additionally, there is a male predominance in the enrolled subjects, which is another study limitation. Subsequent studies will further evaluate its efficacy and safety in patients with asthma and other inflammatory diseases, ensuring more comprehensive and robust findings.

5. Conclusion

MG-ZG122, a novel long-acting humanized anti-TSLP mAb, was safe and well tolerated in Chinese healthy subjects after a single SC injection in a dose ranging from 52.5 mg to 420 mg, and its long half-life may support a once-every 6-month administration. This study provides dosing evidence for subsequent efficacy assessments.

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Disclosure statement

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Author contributions statement

CH Zhang and W Hu made contributions to the conception of the work; X Zhang and LQ Zhang made contributions to the study design and performance; Q Zhang., L Zheng., and JL Guo made contributions to the data acquisition, and interpretation; QL Zou, and R Yan made contributions to analysis, Q Di. performed the interpretation of data; X Zhang and LQ Zhu have drafted the work; CH Zhang and W Hu revised the draft; All authors reviewed and approved the manuscript.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the D Qin, Employee of the sponsor of this work, Hunan Mabgeek Biotech Co., Ltd on reasonable request.

Ethical statement

We confirmed that written informed consent was obtained from each subject before study entry. We have carefully reviewed the entire manuscript and confirm that no information that could potentially identify any individual participant (such as names, contact details, unique demographic identifiers, or any other personally identifiable data).

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