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CLINICAL TRIAL REPORT

Safety, Tolerability, and Pharmacokinetics of HBM9378 (SKB378/WIN378), a Fully Human IgG1 Monoclonal Antibody Against TSLP After Single Ascending Doses in Chinese Healthy Subjects

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Purpose: HBM9378 (SKB378/WIN378) is a novel monoclonal antibody targeting thymic stromal lymphopoietin (TSLP), characterized by an extended half-life and developed to address the unmet medical need for a more durable and convenient biologic therapy for asthma. This first-in-human (FIH) study was conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and immunogenicity of HBM9378 in healthy subjects, providing essential human data to support further clinical development.

Participants and Methods: This Phase I study utilized a single ascending dose (SAD) design with randomization, double-blinding, and placebo control. Five dose-escalation cohorts were included: 20 mg, 60 mg, 200 mg, 600 mg, and 900 mg. Each cohort comprised ten healthy subjects, of whom eight received HBM9378 at the assigned dose and two received placebo. Safety was evaluated through monitoring of adverse events and laboratory assessments. Pharmacokinetics (PK) were characterized by calculating and comparison of key PK parameters. Immunogenicity was assessed by determining the incidence of anti-drug antibody (ADA) following administration.

Results: The safety profiles of the HBM9378 dose groups were comparable to those of the placebo group with respect to treatment-emergent adverse events (TEAEs), and no dose-dependent increase in safety risk was observed. The median T_{max} was 4.05–14.1 days and the mean $T_{1/2}$ was 55.0–65.8 days. HBM9378 exposure (C_{max} and AUC) increased dose-proportionally across the 20–900 mg dose range, and the ADA incidence during the study was 5% (2/40).

Conclusion: HBM9378 was well-tolerated and exhibited a prolonged half-life in healthy subjects. These results support further investigation of HBM9378 in patients with severe immunological disorders.

Trial Registration: This trial was registered on ClinicalTrials.gov (NCT05790694) and on the China Center for Drug Evaluation (CDE) platform (CTR20221961).

Keywords: TSLP, half-life extension, asthma, pharmacokinetics, safety

Introduction

Asthma is a prevalent chronic airway disorder characterized by bronchial hyperreactivity, variable airflow obstruction, and respiratory symptoms. The clinical manifestation, underlying mechanisms and therapeutic responses in asthma are

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considerably heterogeneous,[1–6] affecting 5–10% of the global population and imposing a substantial health and socio-economic burden.[2]

Thymic stromal lymphopoietin (TSLP) is produced by various cell types and plays a crucial role in mediating environmentally triggered inflammation through multiple signaling pathways.[7–10] As a key mediator of asthma pathogenesis,[11–14] TSLP activates both innate and adaptive immune cascades that contribute to asthmatic inflammation. Elevated TSLP levels in asthma are associated with increased Th2 chemokine and greater disease severity.[15–17] Hence, TSLP inhibitors have emerged as clinically validated therapeutic strategies for asthma. Phase II/III studies of tezepelumab, a potent TSLP inhibitor, have demonstrated significant and sustained reductions in asthma exacerbations among patients with severe disease.[18,19] However, limitations remain, including diminished efficacy in patients with lower baseline TSLP levels and unresolved long-term safety uncertainties, such as a higher incidence of serious cardiac adverse events compared to placebo.[20]

HBM9378 (9378/WIN378) is the second fully human IgG1 monoclonal antibody targeting TSLP developed globally, expressed in Chinese hamster ovary (CHO-K1) cells. It may offer substantial therapeutic benefits for individuals with severe asthma. Notably, HBM9378 exhibits a half-life more than twice that of tezepelumab in both monkeys and humans, along with strong stability at high concentrations, favorable druggability, and improved dosing convenience via subcutaneous administration.[20] The extended half-life of HBM9378 enables reduced dosing frequency while maintaining potent TSLP inhibition, potentially enhancing patient adherence and improving control of asthma symptoms and exacerbations. Preclinical studies have demonstrated proof-of-mechanism for HBM9378 in animal models of asthma. Here, we present the results of first-in-human (FIH) study evaluating the safety, tolerability, pharmacokinetics (PK) and immunogenicity of HBM9378 in healthy male and female subjects.

Methods

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The study protocol and informed consent forms were approved by the Ethics Committee of the Chengdu Fifth People's Hospital Affiliated to Chengdu University of Traditional Chinese Medicine (Chengdu, China). Written informed consent was obtained from all subjects prior to study enrollment.

Study Population

Healthy adults (18–50 years, BMI 18–28 kg/m^2) meeting gender-specific weight criteria (≥50 kg for males; ≥45 kg for females) were recruited. All subjects were assessed as healthy based on normal or clinically insignificant findings from required examinations, as determined by the investigator.

Exclusion criteria included: a history of allergic or hypersensitivity reactions, any clinically significant concomitant disease as determined by the investigator; clinical signs of active infection at screening; history of organ transplantation; receipt of immunosuppressive therapy (except topical glucocorticoids) within 6 months prior to randomization; previous exposure to any biological therapy or participation in other clinical trials with study drug administration within 90 days or 5 half-lives of the study drug prior to randomization; use of prescription drugs, health products, herbal supplements, traditional Chinese medicine or over-the-counter drugs within 4 weeks before randomization; immunization within 4 weeks before randomization or planned immunization during the study or within 4 weeks following study completion.

The Safety Analysis Set included all subjects who received any dose of study drug. The PK Analysis Set included all randomized subjects who received any dose of study drug and had at least one valid post-dose drug concentration measurement, while the Immunogenicity Analysis Set comprised randomized subjects who received any dose and had at least one immunogenicity sample test result.

Study Design

This randomized, double-blind, placebo-controlled, single ascending dose (SAD) study evaluated five doses (20, 60, 200, 600, and 900 mg) of HBM9378 administered via subcutaneous (SC) injection versus placebo in healthy volunteers.

As a FIH study of HBM9378, five cohorts (20, 60, 200, 600, 900 mg) were pre-specified, including two *Sentinel Cohorts* (20 mg and 900 mg) and three *Regular Cohorts* (60, 200, 600 mg). In the Sentinel Cohorts (Cohort 1 and 5) the

Table 1 Administration Schema

Cohort	Cohort Setting	Dose (mg)	Subjects Number		Dosing Time
			HBM9378 (SKB378)	Placebo	
1	Sentinel	20	8	2	Day 1
2	Regular	60	8	2	Day 1
3	Regular	200	8	2	Day 1
4	Regular	600	8	2	Day 1
5	Sentinel	900	8	2	Day 1

first two subjects were randomized to receive HBM9378 or placebo at a 1:1 ratio. Following confirmation of safety in these sentinel subjects, the remaining eight subjects were randomized to receive HBM9378 or placebo at a 7:1 ratio. In each *Regular Cohort* (Cohort 2, 3 and 4), all ten subjects were randomized to receive HBM9378 or placebo at an 8:2 ratio. Dose escalation decisions were made based on a blinded review of safety and tolerability data through visit 8 (inclusive) for all dosed subjects in the preceding cohort. Detailed cohort and dosing information is presented in Table 1.

This study was exploratory and did not involve formal hypothesis testing; therefore, no formal sample size calculation was performed. A fixed sample size of 50 subjects (10 per cohort) was planned. A cohort size of 10 subjects (8 active: 2 placebo) facilitates blinded placebo control to better distinguish drug-related adverse events from background events, allows detection of common safety signals, and provides sufficient pharmacokinetic data for reliable initial modeling and parameter estimation. This approach is a pragmatic, historically established standard supporting safe and efficient dose escalation.

Pharmacokinetic (PK) and Immunogenicity Sample Collection

In cohorts 1, 2 and 3, blood samples were collected at predetermined time points to measure serum concentrations of HBM9378. PK samples were collected at predose on Day 1 and at 4 hours, 24 hours, 48 hours, 96 hours, 168 hours, Day 15, Day 29, Day 43, Day 57, Day 85 and Day 113 postdose. Immunogenicity samples were collected at predose on Day 1 and on Day 29, Day 85 and Day 113 postdose. In Cohorts 4 and 5, PK samples were collected at predose on Day 1 and at 4 hours, 24 hours, 48 hours, 96 hours, 168 hours, Day 15, Day 29, Day 43, Day 57, Day 85, Day 113, Day 169 and Day 225 postdose. Immunogenicity samples were collected at predose on Day 1 and on Day 29, Day 85, Day 169 and Day 225 postdose. All samples were processed according to the lab manual and stored at −80°C until transfer to the central lab for analysis.

Pharmacokinetic Assessments

Serum concentrations of HBM9378 were measured using a fully validated enzyme-linked immunosorbent assay (ELISA). The assay utilized the drug target (TSLP), which was coated onto 96-well ELISA plates to capture HBM9378. Bound HBM9378 was detected with a specific detection antibody, followed by Goat anti-Mouse IgG conjugated to horseradish peroxidase (HRP). Tetramethylbenzidine (TMB) substrate solution was added for color development, which was terminated by the addition of 2N sulfuric acid. Absorbance was measured at 450 nm and 620 nm using a Molecule Devices SpectraMax plate reader. Serum concentrations of HBM9378 were determined by non-linear regression curve. The quantification range of the assay was 40.0–2000 ng/mL.

PK parameters were calculated using a non-compartment model with Phoenix WinNonlin version 8.4 (Certara, L.P., Princeton, NJ, USA). Key PK parameters included maximum observed serum concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve (AUC) from time zero to the last measurable concentration (AUC_{last}) and to infinity ($AUC_{0-\infty}$), terminal elimination half-life ($T_{1/2}$), apparent total clearance (CL/F), and apparent volume of distribution (Vd/F). AUC calculations employed the Linear Up Log Down method.

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Anti-Drug Antibody (ADA) Assessments

ADA levels were measured using a fully validated electrochemiluminescence (ECL) assay employing a bridging design. Anti-HBM9378 antibodies present in human serum were captured on ELISA plates pre-coated with HBM9378 and subsequently incubated with ruthenium-labeled HBM9378 and biotin-labeled HBM9378, forming a "biotinylated-HBM9378-ADA-HBM9378-ruthenylated" complex. The complex was then transferred to Streptavidin-coated Meso Scale Discovery (SA-MSD) plates. Following incubation and the addition of MSD read buffer, electrochemiluminescent signals were detected using an MSD reader.

The ADA incidence was evaluated in all subjects who received the active drug.

Safety and Tolerability Assessments

Safety and tolerability were evaluated based on treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory parameters, vital signs, physical examinations, and electrocardiograms (ECGs). All TEAEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 and their severity was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The causal relationship between study treatment and each TEAE was assessed as either Related or Not Related.

Statistical Analysis

Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Inc). Demographic characteristics, PK parameters, immunogenicity results and Adverse events (AEs) were summarized using descriptive statistics for continuous variables and frequency counts (number and percentage of subjects) for categorical variables. Dose proportionality across the evaluated dose range was assessed based on the PK parameters C_{max} and AUC. The linear relationship between the natural logarithm-transformed PK parameters (C_{max} or AUC) and the natural logarithm-transformed dose received in mg was evaluated using a power model, expressed as: log(PK parameter) = $\alpha + \beta \cdot \log(\text{dose}) + \varepsilon$, where α is the intercept, β represents the slope and ε denotes error term. Among them, the slope (β) reflects the relationship between the PK parameter and dose. Estimated slope (β) values with their corresponding 90% confidence intervals were provided. PK Analysis Set, as defined in the method section, was utilized for dose proportionality assessment. In the dataset, BLQ (below limit of quantification) prior to C_{max} were set to 0, and those after C_{max} were set to "ND" before PK parameter calculation for modelling.

Results

Study Population

A total of 209 healthy subjects were screened, of whom 50 were enrolled in the study, as depicted in Figure 1. Of these, 40 subjects received HBM9378 and 10 received placebo. Forty-eight subjects completed the study. One subject from Cohort 4 was found to be pregnant on Day 175 (with an estimated conception date on Day 136), underwent elective abortion on Day 179, and was subsequently withdrawn prematurely from the study on Day 188. Another subject from the placebo cohort was withdrawn due to an AE of ruptured ectopic pregnancy. The mean (SD) age of the enrolled subjects was 27 (5.3) years, ranging from 20 to 41 years. Among the subjects, 70.0% were male and 30.0% were female, all were of Asian descent. Regarding smoking status, 48 subjects (96.0%) were never smokers while 2 subjects (4.0%) were former smokers. Demographics and baseline characteristics are presented in Table 2, all groups exhibited comparable and well-balanced baseline characteristics.

Exposure of HBM9378

Exposure to HBM9378 is summarized in Table 3. All 50 subjects completed administration of the study drug (HBM9378 or placebo), achieving a treatment compliance rate of 100% with no interruptions in dosing. Subjects in Cohorts 1, 2 and 3 were followed for 107 to 115 days post-injection, while those in Cohorts 4 and 5 were followed for 188 to 225 days.

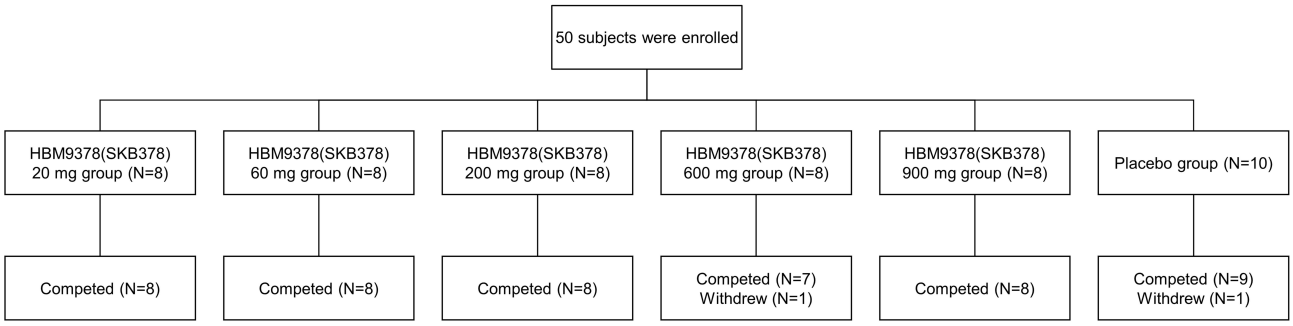

Figure 1 Subject Disposition.

Note: Inclusion Criteria: healthy Chinese male and females aged ≥18 and ≤50 years, males weight ≥50 kg, females ≥45 kg, and all subjects with body mass index (BMI) 18–28 kg/m^2; females of non-childbearing potential, or negative blood pregnancy test result at screening and agree to follow effective contraceptive measures if with childbearing potential, or males or their heterosexual partners agree to use effective contraceptive methods during the study participation Study Endpoints: Primary Endpoints 1) Safety and tolerability (include physical examination, vital signs, ECG, lab safety parameters, injection site reaction, AEs, SAEs), 2) Pharmacokinetics (include C_{max}, T_{max}, AUC_{last}, $AUC_{0-\infty}$, $T_{1/2}$, CL/F, V_d/F), and Secondary Endpoint 1) Immunogenicity (include ADA positive rate).

Safety

Among subjects receiving HBM9378 and placebo, 36 (90.0%) and 9 (90.0%) subjects experienced TEAEs, respectively, while 24 (60.0%) and 6 (60.0%) subjects experienced treatment-related adverse events (TRAEs). All TEAEs in the HBM9378 dose groups were Grade 1 or 2 in severity; no SAEs, deaths, or TEAEs leading to discontinuation of HBM9378 were reported. In the placebo group, no TEAEs resulted in discontinuation or death. One subject in placebo group experienced a Grade 4 TEAE (Subject ID: 1001171, Preferred Term: ruptured ectopic pregnancy, which was also reported as a SAE and led to withdraw from the study; this event was unrelated to placebo administration). No injection site reactions were observed in any dose group. Except for the Grade 4 ruptured ectopic pregnancy, all other TEAEs were Grade 1–2 and most resolved spontaneously without medical intervention.

TRAEs with an incidence of ≥5% in any HBM9378 dose group compared to placebo are summarized in Table 4. By worst CTCAE grade, all TRAEs were Grade 1 except for two Grade 2 TRAEs, each occurring in one subject from the 20 mg and 200 mg groups. The Grade 2 TRAEs were acute pericoronitis (Preferred Term: Pericoronitis) in the HBM9378 20 mg group, which occurred on Day 53 and resolved on Day 59 following treatment with ornidazole, and liver enzymes elevations (Preferred Term: Alanine aminotransferase increased, Aspartate aminotransferase increased, and Gamma-glutamyltransferase increased) in the HBM9378 200 mg group, which occurred on Day 85, were not associated with increases in bilirubin or alkaline phosphatase and resolved with hepatoprotective therapy (bicyclol and polyene phosphatidylcholine). No other subjects developed liver enzyme elevations during the study period. All TRAEs in the placebo group were Grade 1.

Pharmacokinetics

Serum concentrations of HBM9378 post single SC dose were measured in the 40 subjects received HBM9378. PK parameters are summarized in Table 5, and PK profiles are presented in Figure 2 and 3. Following a single SC injection of 20 mg, 60 mg, 200 mg, 600 mg, and 900 mg HBM9378, the median T_{max} ranged from 4.05–14.1 days. The mean C_{max} (mean ± SD) was 1.71 ± 0.2171, 5.12 ± 1.593, 22.3 ± 6.892, 54.2 ± 17.64 and 114 ± 19.94 μg/mL, respectively. The mean AUC_{last} (mean ± SD) was 122 ± 17.40, 332 ± 85.24, 1240 ± 280.9, 4740 ± 1254 and 8550 ± 1728 μg·day/mL, respectively. The mean $AUC_{0-\infty}$ (mean ± SD) for 20, 200, 600 and 900 mg cohorts was 156 ± 20.88, 1730 ± 419.4, 5100 ± 1362 and 9430 ± 2220 μg·day/mL, respectively. Due to the small sample size in 60 mg cohort (n = 2), the $AUC_{0-\infty}$ [mean (minimum, maximum)] was reported as 467 (463, 471) μg·day/mL. Exposure to HBM9378 (C_{max} and AUC) increased in a dose-proportional manner across the 20–900 mg dose range.

The coefficient of variation (CV%) of C_{max} for HBM9378 ranged from 12.68% to 32.57%, and for AUC (both AUC_{last} and $AUC_{0-\infty}$) ranged from 13.40% to 26.70%, indicating low to moderate variability for HBM9378.

The mean clearance (CL/F) ranged from 0.101 to 0.130 L/day across dose groups; the mean apparent volume of distribution (V_d/F) ranged from 8.54 to 11.0 L; and the mean half-life ($T_{1/2}$) ranged from 55.0 to 65.8 days.

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Table 2 The Demographics and Baseline Characteristics

	HBM9378 (SKB378)					Placebo (N = 10)	Total (N = 50)
	Cohort 1: 20 mg (N = 8)	Cohort 2: 60 mg (N = 8)	Cohort 3: 200 mg (N = 8)	Cohort 4: 600 mg (N = 8)	Cohort 5: 900 mg (N = 8)		
Age (years)							
Mean (SD)	25 (3.3)	31 (6.8)	26 (6.0)	25 (2.0)	28 (5.6)	29 (5.3)	27 (5.3)
Median (Q1, Q3)	26 (23, 27)	30 (26, 38)	24 (22, 28)	25 (25, 27)	27 (24, 33)	27 (26, 33)	26 (24, 29)
Sex N (%)							
Male	6 (75.0%)	4 (50.0%)	7 (87.5%)	5 (62.5%)	6 (75.0%)	7 (70.0%)	35 (70.0%)
Female	2 (25.0%)	4 (50.0%)	1 (12.5%)	3 (37.5%)	2 (25.0%)	3 (30.0%)	15 (30.0%)
Race N (%)							
Asian	8 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	10 (100%)	50 (100%)
Other	0	0	0	0	0	0	0
Height (cm)							
Mean (SD)	167.4 (3.19)	162.4 (8.51)	169.1 (6.79)	165.3 (6.95)	169.4 (4.27)	165.6 (8.92)	166.5 (6.95)
Median (Q1,Q3)	168.0 (164.5, 169.3)	162.8 (156.0, 167.0)	167.8 (165.0, 174.0)	165.0 (160.3, 170.8)	168.5 (166.3, 171.8)	167.0 (157.5,173.0)	167.0 (163.0, 171.5)
Weight (kg)							
Mean (SD)	63.2 (7.59)	56.4 (4.85)	63.9 (8.54)	62.0 (11.13)	62.8 (9.94)	60.7 (5.81)	61.5 (8.13)
Median (Q1, Q3)	62.1 (58.6, 68.4)	53.9 (53.3,58.8)	64.7 (59.1, 69.8)	60.8 (52.4, 66.2)	60.1 (55.8, 66.6)	61.6 (55.7, 66.2)	60.7 (54.2, 66.2)
BMI (kg/m^2)							
Mean (SD)	22.5 (2.24)	21.5 (1.82)	22.3 (2.39)	22.6 (2.69)	21.9 (2.91)	22.2 (1.52)	22.1 (2.20)
Median (Q1, Q3)	21.6 (21.4, 24.2)	21.2 (20.1, 23.1)	23.0 (19.9, 24.2)	22.6 (20.2, 23.7)	21.4 (19.4, 24.1)	21.9 (21.3, 22.6)	22.0 (20.5, 23.6)

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Table 3 Exposure of HBM9378 (SKB378)

	HBM9378 (SKB378)					Placebo	Total
	Cohort 1: 20 mg	Cohort 2: 60 mg	Cohort 3: 200 mg	Cohort 4: 600 mg	Cohort 5: 900 mg		
	(N = 8)	(N = 8)	(N = 8)	(N = 8)	(N = 8)	(N = 10)	(N = 50)
Infusion to end of follow-up (Days)[a]							
Mean (SD)	107 (0.7)	113 (0)	113 (0.7)	220 (13.1)	221 (2.3)	157 (58.6)	155 (54.8)
Min, Max	107, 109	113, 113	113, 115	188, 225	219, 225	107, 228	107, 228
Average dose (mL)							
Mean (SD)	0.14 (0)	0.4 (0)	1.34 (0)	4 (0)	6 (0)	2.38 (2.392)	2.38 (2.292)
Min, Max	0.14, 0.14	0.4, 0.4	1.34, 1.34	4, 4	6, 6	0.14, 6	0.14, 6
Compliance[b]							
Mean (SD)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)
Min, Max	100, 100	100, 100	100, 100	100, 100	100, 100	100, 100	100, 100
<80%	0	0	0	0	0	0	0
80%–<125%	8 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	10 (100%)	50 (100%)
≥125%	0	0	0	0	0	0	0
Infusion status							
Finished	8 (100%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)	10 (100%)	50 (100%)
Interrupted	0	0	0	0	0	0	0

Notes: [a] Infusion to end of follow-up = date of study completion or early withdrawal - date of dose + 1.[b] Compliance (%) = actual dose (mL)/planned dose (mL) × 100.

Dose-Exposure Proportionality

Results from the power model analysis are shown in Table 6. The β value for $AUC_{0-\infty}$ was 1.05 (90% confidence interval: 1.00–1.10), and the β value for C_{max} was 1.07 (90% confidence interval: 1.02–1.13), indicating that exposure (C_{max} and AUC) increased near dose-proportionally over the range of 20–900 mg.

Immunogenicity Analysis

ADA results for each dose group following SC injection of HBM9378 are summarized in Table 7. Two subjects tested positive for ADA; both were treatment-induced ADA and exhibited low titers. One subject in the 20 mg cohort was ADA-positive on Day 85 but reverted to negative on Day 113. Another subject in the 60 mg cohort was ADA-positive on Day 113 (end of study). The overall incidence of ADA was 5.0% (2/40).

Discussion

This study provides preliminary safety data in humans and a comprehensive evaluation of the PK characteristics following single escalating doses of HBM9378, a fully human IgG1 monoclonal antibody targeting TSLP.

Overall, HBM9378 was safe and well tolerated after a single SC injection of 20 to 900 mg in healthy Chinese subjects. The incidence of TEAEs in the HBM9378 dose groups was the same compared to that in the placebo group. Except for a single case of ruptured ectopic pregnancy requiring hospitalization in the placebo group, all other TEAEs were Grade 1–2. No SAEs, deaths, or TEAEs leading to study discontinuation or withdrawal occurred in any of the HBM9378 dose groups. No injection site reactions or hypersensitivity-related AEs were observed in either the HBM9378 or placebo groups. There was no evidence of an increased safety risk associated with escalating doses of HBM9378. In contrast to products of the same mechanism of action (MOA) such as tezepelumab, commonly reported adverse reactions of pharyngitis, arthralgia, back pain and hypersensitivities including rash were not observed in this study. Only one subject from 20 mg group reported treatment-related Grade 1 conjunctivitis. However, due to the limited clinical data available, the safety profile of HBM9378 is not yet fully established, which may partly explain differences in observed adverse event types.

Table 4 Summary of TRAEs with Higher Incidence (≥5%) in Any Dose Group of HBM9378 (SKB378) Compared with Placebo

Category	HBM9378 (SKB378)						Placebo (N = 10) n (%)
	Cohort 1: 20 mg (N = 8) n (%)	Cohort 2: 60 mg (N = 8) n (%)	Cohort 3: 200 mg (N = 8) n (%)	Cohort 4: 600 mg (N = 8) n (%)	Cohort 5: 900 mg (N = 8) n (%)	Total (N = 40) n (%)	
AE Summary							
TEAE	8 (100)	8 (100)	6 (75.0)	8 (100)	6 (75.0)	36 (90.0)	9 (90.0)
≥ Grade 3 TEAE	0	0	0	0	0	0	1 (10.0)
TRAE	5 (62.5)	4 (50.0)	6 (75.0)	6 (75.0)	3 (37.5)	24 (60.0)	6 (60.0)
≥ Grade 3 TRAE	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	1 (10.0)
Treatment-related SAE	0	0	0	0	0	0	0
Summary of TRAEs with Higher Incidence (≥5%) in Any Dose Group of HBM9378 (SKB378) Compared with Placebo							
System Organ Class/Preferred Term							
Investigations	4 (50.0)	4 (50.0)	5 (62.5)	6 (75.0)	3 (37.5)	22 (55.0)	3 (30.0)
White blood cells urine positive	0	2 (25.0)	1 (12.5)	3 (37.5)	1 (12.5)	7 (17.5)	1 (10.0)
Alanine aminotransferase increased	1 (12.5)	0	3 (37.5)	1 (12.5)	1 (12.5)	6 (15.0)	0
Red blood cells urine positive	2 (25.0)	1 (12.5)	0	1 (12.5)	1 (12.5)	5 (12.5)	0
Urinary occult blood positive	1 (12.5)	1 (12.5)	0	2 (25.0)	0	4 (10.0)	0
Gamma-glutamyltransferase increased	0	0	2 (25.0)	0	0	2 (5.0)	0
Blood uric acid increased	1 (12.5)	0	0	0	1 (12.5)	2 (5.0)	0
Low density lipoprotein increased	0	0	0	1 (12.5)	0	1 (2.5)	0
Lymphocyte count decreased	1 (12.5)	0	0	0	0	1 (2.5)	0
Protein urine present	0	1 (12.5)	0	0	0	1 (2.5)	0
Urobilinogen urine increased	0	0	1 (12.5)	0	0	1 (2.5)	0
Basophil percentage increased	0	0	0	0	1 (12.5)	1 (2.5)	0
Aspartate aminotransferase increased	0	0	1 (12.5)	0	0	1 (2.5)	0
Electrocardiogram ST segment depression	0	1 (12.5)	0	0	0	1 (2.5)	0
Blood triglycerides increased	0	0	0	1 (12.5)	0	1 (2.5)	0
Infections and infectious diseases	3 (37.5)	1 (12.5)	1 (12.5)	1 (12.5)	0	6 (15.0)	4 (40.0)
Pericoronitis	1 (12.5)	0	0	0	0	1 (2.5)	0
Conjunctivitis	1 (12.5)	0	0	0	0	1 (2.5)	0

Abbreviations: TEAE, Treatment-emergent adverse event; TRAE, Treatment-related adverse event; SAE, Serious adverse event.

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Table 5 Pharmacokinetic Parameters of HBM9378 (SKB378) After Single Dose Subcutaneous Injection (PKS)

Parameter	HBM9378 (SKB378)									
	Cohort 1: 20 mg		Cohort 2: 60 mg		Cohort 3: 200 mg		Cohort 4: 600 mg		Cohort 5: 900 mg	
	n	(N = 8)	n	(N = 8)	n	(N = 8)	n	(N = 8)	n	(N = 8)
C_{max} (μg/mL)	8	1.71 ± 0.2171 (12.68%)	8	5.12 ± 1.593 (31.09%)	8	22.3 ± 6.892 (30.87%)	8	54.2 ± 17.64 (32.57%)	8	114 ± 19.94 (17.46%)
T_{max} (day)	8	10.5 (7.06, 28.1)	8	14.1 (7.07, 28.1)	8	7.06 (2.00, 28.1)	8	7.05 (4.05, 28.1)	8	4.05 (4.03, 14.1)
AUC_{last} (μg·day/mL)	8	122 ± 17.40 (14.30%)	8	332 ± 85.24 (25.67%)	8	1240 ± 280.9 (22.64%)	8	4740 ± 1254 (26.45%)	8	8550 ± 1728 (20.20%)
$AUC_{0-\infty}$ (μg·day/mL)	6	156 ± 20.88 (13.40%)	2	467 (463, 471)	3	1730 ± 419.4 (24.19%)	8	5100 ± 1362 (26.70%)	8	9430 ± 2220 (23.55%)
$T_{1/2}$ (day)	6	55.0 ± 12.53 (22.77%)	2	58.9 (55.4, 62.3)	3	65.8 ± 16.23 (24.65%)	8	56.0 ± 3.091 (5.520%)	8	61.4 ± 13.13 (21.38%)
CL/F (L/day)	6	0.130 ± 0.01662 (12.82%)	2	0.128 (0.127, 0.129)	3	0.121 ± 0.03179 (26.38%)	8	0.125 ± 0.03334 (26.58%)	8	0.101 ± 0.02590 (25.71%)
V_d/F (L)	6	10.1 ± 1.729 (17.08%)	2	10.9 (10.3, 11.4)	3	11.0 ± 1.935 (17.53%)	8	10.1 ± 2.701 (26.68%)	8	8.54 ± 0.7545 (8.838%)

Notes: N represents the number of subjects enrolled, and n represents the number of subjects included in descriptive statistics. The summary results of each parameter are presented as follows: T_{max} is presented as median (minimum, maximum); Other parameters were presented as arithmetic mean ± standard deviation (arithmetic CV%) when n ≥3 and presented as arithmetic mean (minimum, maximum) when n = 2.

In this study, the overall incidence of TRAEs in the HBM9378 group was the same compared to that in the placebo group (60.0% vs. 60.0%), as shown in Table 4. The most frequently reported TRAEs in HBM9378 recipients were transient Grade 1–2 laboratory abnormalities – including white blood cells urine positive (17.5%), alanine aminotransferase increased (15.0%), red blood cells urine positive (12.5%), and urinary occult blood positive (10.0%) – with no

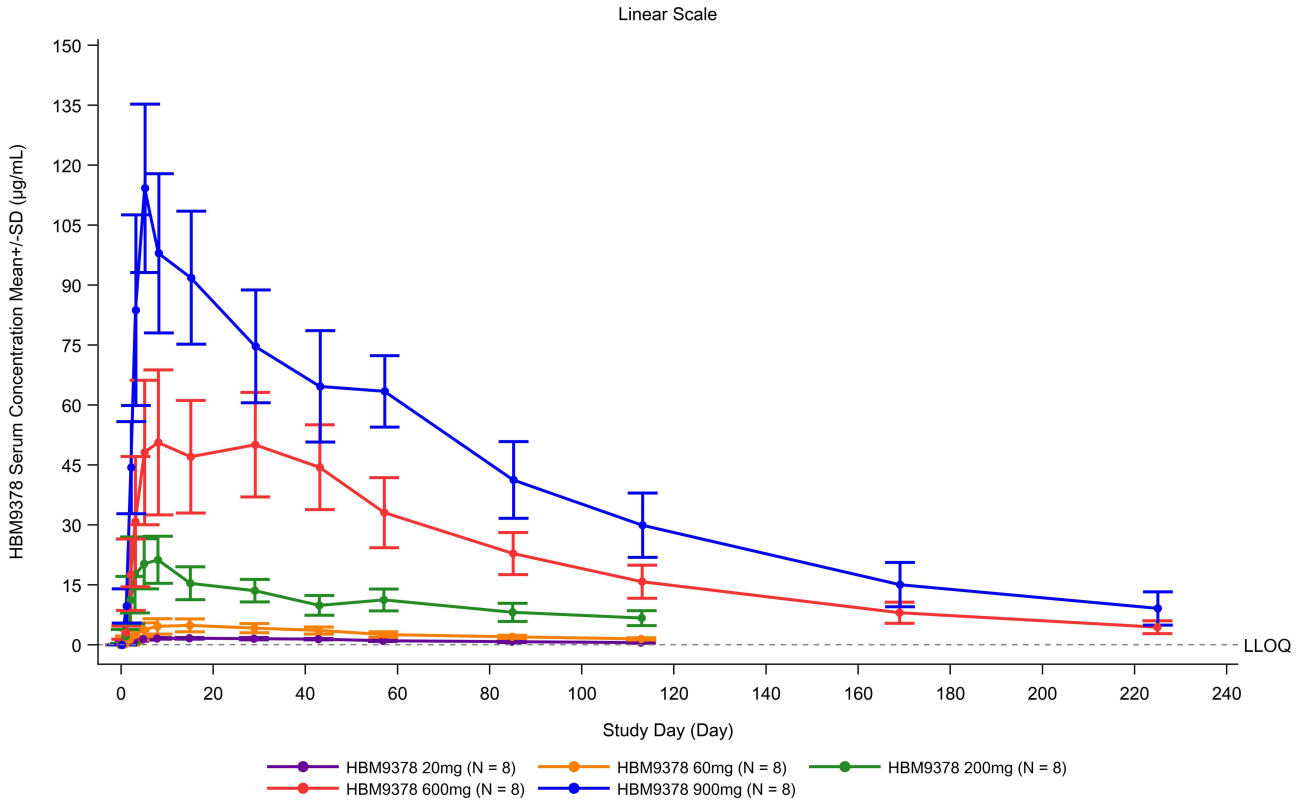

Figure 2 Mean Serum Concentration-Time Curves of HBM9378 in Subjects After a Single Subcutaneous Injection in Each Dose Group (Linear Scale; Semi-Logarithmic Scale).
Notes: LLOQ (lower limit of quantitation) is 0.04 μg/mL. For concentration with BLQ, set to zero in linear scale graph and omitted on log scale graph.

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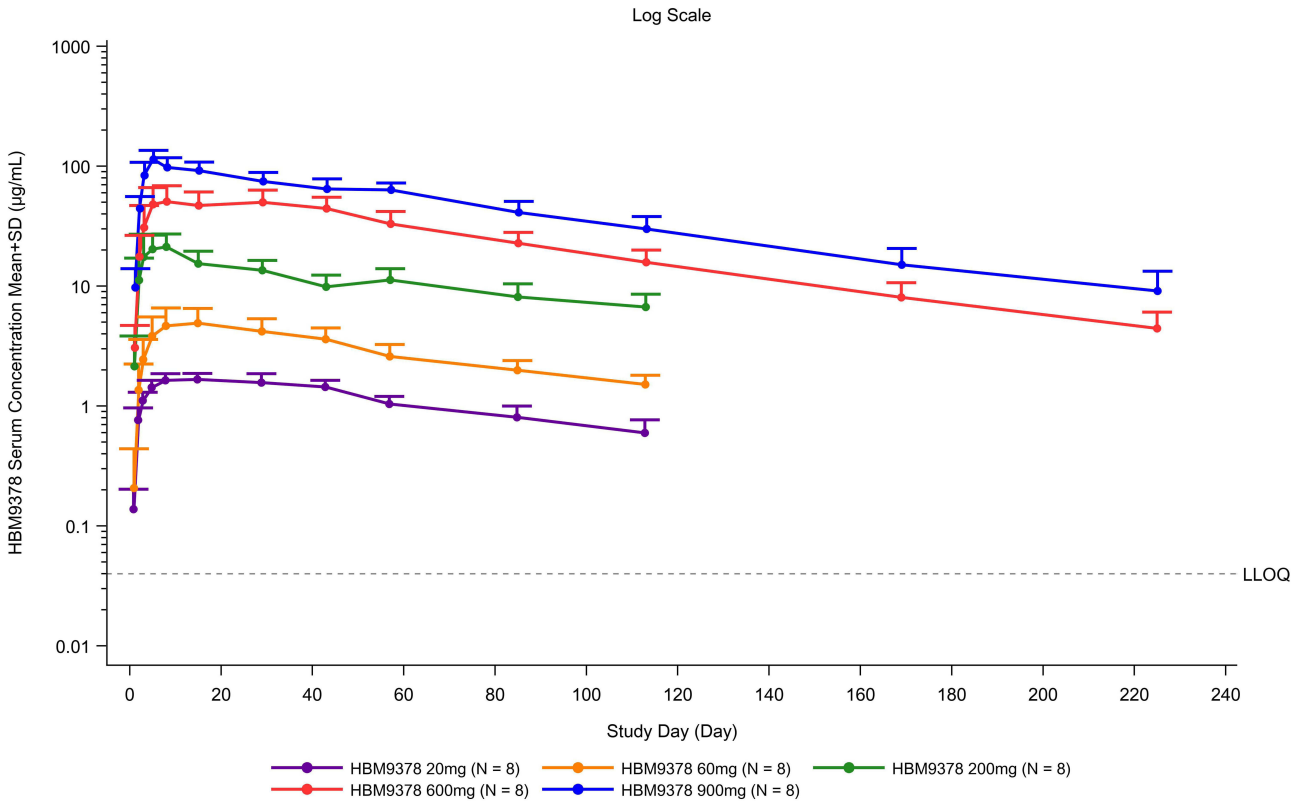

Figure 3 Mean Serum Concentration-Time Curves of HBM9378 in Subjects After a Single Subcutaneous Injection in Each Dose Group (Semi-Logarithmic Scale).
Notes: LLOQ (lower limit of quantitation) is 0.04 μg/mL. For concentration with BLQ, set to zero in linear scale graph and omitted on log scale graph.

clear dose relationship observed. These findings were not associated with nonclinical safety signals or known class effects of TSLP inhibition; while possible explanations such as mild urinary tract infection or undiagnosed lithiasis cannot be excluded, causality remains uncertain given the small sample size and healthy-volunteer context.

The PK profile of HBM9378 was characterized in 40 healthy subjects. Following single SC doses ranging from 20 mg to 900 mg, exposure (C_{max} and AUC) increased near dose-proportionally with dose escalation. The mean $T_{1/2}$ was 55.0–65.8 days, substantially longer than that reported for tezepelumab (19.9–25.7 days).[21] This extended half-life may be attributable to molecular modifications within the Fc domain of HBM9378. The recommended dosing regimen for tezepelumab in severe asthma is 210 mg every 4 weeks; the extended half-life of HBM9378 may allow for less frequent administration in clinical practice, potentially improving patient adherence and convenience during long-term treatment.

Immunogenicity was also evaluated following a single SC injection of HBM9378 in 40 healthy subjects. Only two subjects tested positive for ADA – one each in the 20 mg and 60 mg cohorts – resulting in an overall ADA incidence of 5.0%. Both cases involved low-titer, treatment-induced ADA responses; notably, ADA positivity did not impact PK exposure in these subjects. The incidence and clinical impact of ADAs after multiple dosing and in patient populations remain to be determined in future studies.

Table 6 Evaluation of Dose-Exposure Ratio

Parameter	Dose range	n	Slope	90% Confidence Interval	*P* Value
$AUC_{0-\infty}$ (μg·day/mL)	20 mg-900 mg	27[a]	1.05	(1.00, 1.10)	<0.0001
C_{max} (μg/mL)	20 mg-900 mg	40[b]	1.07	(1.02, 1.13)	<0.0001
AUC_{last} (μg·day/mL)	20 mg-900 mg	40[b]	1.12	(1.07, 1.16)	<0.0001

Note: [a] n = 27; 6, 2, 3, 8, and 8 subjects in the 20, 60, 200, 600, and 900 mg cohorts were included in the statistical analysis, respectively.[b] n = 40; all subjects who received HBM9378 and had evaluable PK samples.

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Table 7 ADA Results of HBM9378 (SKB378) After Single Dose Subcutaneous Injection

	HBM9378 (SKB378)				
	Cohort 1: 20 mg (N = 8) n (%)	**Cohort 2: 60 mg (N = 8) n (%)**	**Cohort 3: 200 mg (N = 8) n (%)**	**Cohort 4: 600 mg (N = 8) n (%)**	**Cohort 5: 900 mg (N = 8) n (%)**
Subjects with at least one ADA data	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)
Subjects with at least one post treatment ADA	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)
ADA positive	1 (12.5)	1 (12.5)	0	0	0
Baseline ADA positive	0	0	0	0	0
Treatment-Enhanced ADA	0	0	0	0	0
Post-Baseline ADA positive	1 (12.5)	1 (12.5)	0	0	0
Treatment-Induced ADA	1 (12.5)	1 (12.5)	0	0	0
ADA negative	7 (87.5)	7 (87.5)	8 (100)	8 (100)	8 (100)

Notes: ADA positive is defined as subjects with at least one positive ADA. Treatment-Enhanced ADA is defined as subjects who had a baseline-positive ADA results and at least one enhanced result (greater than 4-folder of baseline-positive ADA titer) at any time after first drug administration. Treatment-Induced ADA is defined as subjects who had a baseline-negative ADA results and at least one positive ADA results at any time after first drug administration. ADA negative is defined as subjects with all ADA negative results.

Abbreviation: ADA, anti-drug antibody.

A limitation of this study is the inability to evaluate biomarkers of disease activity due to enrollment of healthy subjects. Additionally, a gender imbalance (approximately 70% male), and the enrolled population was predominately young (mean age approximately 27 years), potentially reducing age-related variability and limiting extrapolation to older adults where metabolic differences may influence PK/PD and safety profiles. Future studies involving broader and more diverse populations are warranted to establish comprehensive dosing recommendations and safety profiles across all patient populations. Earlier clinical data with Tezepelumab, including DESTINATION, raised concerns for certain cardiac events, but longer-term follow-up did not confirm a clear cardiovascular safety signal. In this SAD healthy-volunteer study of HBM9378, no major adverse cardiovascular events were observed. Future studies will include scheduled ECGs, systematic assessment and prompt reporting of cardiovascular symptoms, and event adjudication as appropriate to ensure comprehensive cardiac safety monitoring.

Conclusion

HBM9378 was safe and well-tolerated in healthy subjects and exhibited a long half-life that may allow reduced dosing frequency and improved adherence compared to existing therapies. The low incidence of ADA suggests minimal impact of immunogenicity on PK profiles.

Further studies are warranted to evaluate its safety, tolerability, PK, immunogenicity and efficacy of HBM9378 following repeated dosing in patients with asthma and related inflammatory airway disease mediated by the TSLP pathway.

Data Sharing Statement

All data supporting the findings of this study are available within the manuscript. Additional data are available upon reasonable request from the corresponding author (Wen He). Any shared data will be deidentified to protect participant confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Nan Cao, Shuai Zhao, Yuanqing Wei, Jia Lu, Ruixuan Luo and Xiaolu Tao are employees of Harbour BioMed. Junyou Ge is affiliated with Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd./National Engineering Research Center of Targeted Biologics. All other authors report no conflicts of interest in this work.

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