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ARTICLE

A first-in-human, single and multiple dose study of lunsekimig, a novel anti-TSLP/anti-IL-13 NANOBODY® compound, in healthy volunteers

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Abstract

Lunsekimig is a novel, bispecific NANOBODY® molecule that inhibits both thymic stromal lymphopoietin (TSLP) and interleukin (IL)-13, two key mediators of asthma pathophysiology. In this first-in-human study, we evaluated the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of lunsekimig in healthy adult participants. Participants received single ascending doses (SAD) of lunsekimig (10–400 mg intravenous [IV] or 400 mg subcutaneous [SC]) (SAD part) or multiple ascending doses (MAD part) of lunsekimig (100 or 200 mg, every 2 weeks [Q2W] for three SC doses), or placebo. Overall, 48 participants were randomized 3:1 in the SAD part and 4:1 in the MAD part for lunsekimig or placebo. The primary endpoint was safety and tolerability. The secondary endpoints included PK, antidrug antibodies (ADAs) and total target measurement. Lunsekimig was well tolerated and common treatment-emergent adverse events were COVID-19, nasopharyngitis, injection site reactions, and headache. Lunsekimig showed dose-proportional increases in exposure and linear elimination. Mean $t_{1/2z}$ of lunsekimig was around 10 days across all IV and SC doses of the SAD and MAD parts of the study. Increases in the serum concentration of total TSLP and IL-13 for lunsekimig versus placebo indicated target engagement. ADA of low titers were detected in four (11.1%) participants who received lunsekimig in the SAD, and seven (43.8%) in the MAD. In conclusion, lunsekimig was well tolerated in healthy participants with a linear PK profile up to single 400 mg IV and SC dose and multiple doses of 100 and 200 mg SC Q2W, with low immunogenicity.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Anti-TSLP and anti-IL-13 monospecific monoclonal antibodies have been successfully explored for the possible treatment of asthma and atopic dermatitis and shown to be safe and well tolerated with minimal off-target effects. Lunsekimig is the first NANOBODY® compound biologic to block both TSLP and IL-13.

WHAT QUESTION DID THIS STUDY ADDRESS?

This first-in-human, dose escalation, phase I trial aimed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of single and multiple ascending doses of lunsekimig in healthy adult participants.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Lunsekimig, a bispecific anti-TSLP/anti-IL-13 NANOBODY® compound, was well tolerated with an acceptable safety and dose-proportional, linear pharmacokinetic profile up to a single 400 mg IV and SC dose and multiple doses of 100 and 200 mg SC Q2W, with no clinically meaningful immunogenicity.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL MEDICINE?

The findings support the further clinical development of lunsekimig. The efficacy, safety, and tolerability of add-on therapy with lunsekimig in adults with moderate-to-severe asthma are currently being assessed in the phase 2b dose ranging study AIRCULES.

INTRODUCTION

Asthma is a chronic inflammatory airway disease associated with elevated T-helper 2 cytokines (interleukin [IL]-5, IL-13, and IL-4) and eosinophilic airway infiltration.[1] Thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine, acts as an "alarmin" and is an upstream initiator of the airway response to inhaled allergen, irritant, or pathogen. IL-13 is a key Type 2 cytokine which act as a downstream mediator of airway response to insults, amplifying the asthmatic response.[2] Anti-TSLP and anti-IL-13 monospecific monoclonal antibodies (mAbs) have been explored for the possible treatment of asthma and atopic dermatitis and shown to be safe and well tolerated with minimal off-target effects.[3–6] We hypothesize that the dual blockade of TSLP and IL-13 may yield additive and/or synergistic benefits in asthma.

Lunsekimig (SAR443765) is the first bispecific NANOBODY®* molecule in development for asthma and blocks both TSLP and IL-13. NANOBODY® molecules are therapeutic proteins that are based on the smallest functional fragments of heavy-chain-only antibodies, which occur naturally in the Camelidae family (Figure 1). They have a high degree of homology (in terms of sequence and structure) to human immunoglobulin heavy-chain variable regions and can be further engineered and expressed by microbial cells such as *Komagataella phaffii* (*Pichia pastoris*).[7] Approximately, 10 times smaller (12–15 kDa) than mAbs, they are highly stable, high affinity (nM-pM) variable domains (building blocks) that can be fused head-to-tail with amino acid glycine/serine (GS) linkers in a "mix-and-match" form to generate multivalent, multispecific molecules. Lunsekimig is a sequence optimized NANOBODY® molecule consisting five (building blocks) that bind to two IL-13 epitopes, two TSLP epitopes and to human serum albumin for half-life extension via FcRn-mediated recycling. Lunsekimig inhibited the functional effects of TSLP and IL-13 in cytokine-specific assays and in stimulated human peripheral blood mononuclear cell assay systems. In an in vivo mouse model humanized with hematopoietic stem cells and human IL-4 and TSLP mini-circle DNA, lunsekimig significantly reduced plasma human IL-13 and human TSLP concentration from ≥0.01 mg/kg. No direct target organ toxicity was identified in the toxicity studies.

This first-in-human, phase I trial (EudraCT: 2021–000356-19) aimed to assess the safety, tolerability, pharmacokinetic (PK), pharmacodynamics (PD), and immunogenicity of single and multiple ascending doses (MADs) of lunsekimig in healthy adult participants.

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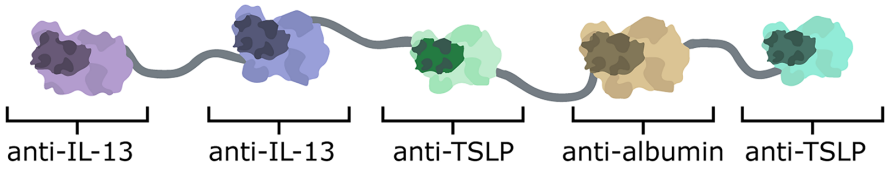

FIGURE 1 A schematic representation of lunsekimig molecular structure. Lunsekimig (SAR443765) is a bispecific anti-TSLP/anti-IL-13 NANOBODY® construct, antagonizing the function of these two soluble human cytokines. It is a pentavalent molecule, consisting of two NANOBODY building blocks, each binding to different epitopes of TSLP, two NANOBODY® building blocks targeting different epitopes of IL-13, and one NANOBODY® building block that binds to human albumin to extend the half-life ($t_{1/2}$). IL, interleukin; TSLP, thymic stromal lymphopoietin.

METHODS

Study design

This was a first-in-human, three-part, phase I, double-blind, randomized, placebo-controlled, parallel design trial (ClinicalTrials.gov, NCT05366764). Parts 1 and 3 were a single ascending dose (SAD) study and multiple ascending dose (MAD) study, respectively, in healthy adult participants conducted at a single center in Berlin, Germany (Figure S1). Part 2 was a single dose study in participants with mild-to-moderate asthma for which the results will be published separately.[8,9] Here, only the data from SAD and MAD parts of the study are presented. Eligible participants were healthy male and female adults, aged 18–45 years with a body mass index of 18–30 kg/m^2 and total body weight of 40–90 kg for females and 50–100 kg for males, inclusive.

Single ascending dose part

Participants were randomized 3:1 in each of the six cohorts ($n=8$; six active and two placebo per cohort) receiving either lunsekimig (10, 30, 90, 200, and 400 mg intravenous [IV; infusion over approximately 1 h] or 400 mg subcutaneous [SC]) or placebo. The starting dose was below the maximum recommended starting dose per FDA guidance with a safety factor of 30 to account for potential synergistic effects of the bispecific approach. The maximal dose was selected to have at least a twofold margin compared with exposure at the no adverse effect level. Dose escalation for all SAD cohorts was based on at least Day 8 safety and tolerability data of the previous dose level cohort. Pharmacokinetic data through at least Day 15 from SAD IV cohorts 1–3 were used to update predicted exposures for SAD IV cohorts 3–5, respectively. All cohorts included two sentinel participants who were dosed on the first day, one sentinel participant received lunsekimig and the other received placebo. The remaining participants from each cohort were dosed in subgroups of maximum three participants per day (with at least 1 h between end of dosing and start of dosing for the next participant), with at least a 2-day safety window between subgroups.

Multiple ascending dose part

Participants were randomized 4:1 in each of the two cohorts ($n=10$; eight active and two placebo per cohort) receiving either lunsekimig (100 or 200 mg SC) or placebo. Lunsekimig was administered subcutaneously every 2 weeks (Q2W) for three doses (Day 1, Day 15, and Day 29). Initiation of the MAD part was based on at least Day 8 safety and tolerability data of the SAD SC cohort. In addition, PK data up to at least Day 15 of the SAD Cohorts 5 (IV) and 6 (SC) were used to make a preliminary assessment of absolute bioavailability and verify exposure predictions for the SC MAD cohorts (SC). Dose escalation for the second cohort was based on Day 8 safety data relative to the last dose of lunsekimig from MAD cohort 1 (corresponding to Day 36). Participants were dosed in subgroups of maximum 5 with inter-participant dosing spaced at least 1 h apart and at least a 2-day safety window between subgroups.

This study was conducted in accordance with Good Clinical Practice and ethical principles of the Declaration of Helsinki. All participants provided written informed consents prior to the first study procedure. The protocols, amendments, and informed consents received appropriate approval from the Institutional Review Board prior to initiation of the study.

Objectives

Primary objectives

Objectives were aligned in both SAD and MAD parts of the study. The primary objective was the safety and tolerability of lunsekimig. The secondary objectives were to assess the PK behavior of lunsekimig in healthy participants following single IV infusion and single or multiple

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SC injections, and the immunogenicity of lunsekimig and the PD effect by measuring target engagement for TSLP and IL-13.

Assessments

Safety

Safety and tolerability assessments included the incidence and frequency of adverse events (AEs), treatment-emergent adverse events (TEAEs) and their severity, adverse events of special interest (AESIs; pregnancy, symptomatic study drug overdose, threefold increase in alanine transaminase, QTcF ≥500 ms, SARS-CoV-2 infection), potentially clinically significant abnormalities of vital signs, physical examinations, clinical laboratory tests and electrocardiogram (ECG) abnormalities. All local injection site reactions were captured as TEAE, regardless of severity or clinical significance. Safety and tolerability were assessed in all participants who received at least one dose of lunsekimig or placebo.

Pharmacokinetics

Pharmacokinetic analysis included data from all participants who received at least one dose of lunsekimig and had at least one primary PK parameter evaluable. Serum samples for PK analyses were collected on Day 1 (0 h [pre-dose], 1, 4, 8 h post-dose for IV cohort; 0 h [pre-dose], 3, 8, 12 h post-dose for SC cohort), Day 2 (24, 32 h post-dose for IV cohort; 24 h post-dose for SC cohort), Day 3, Day 4, Day 5, Day 6, Day 8, Day 15, Day 22, Day 29, Day 43, Day 57, and Day 71 (end of study [EOS]) for the SAD part, and on Day 1 (0 h [pre-dose], 3, 6, 12 h post-dose), Day 2, Day 3, Day 4, Day 8, Day 15 (pre-dose), Day 29 (0 h [pre-dose], 3, 6, 12 h post-dose), Day 30, Day 31, Day 32, Day 36, Day 43, Day 50, Day 71, and Day 99 (EOS) for the MAD part. Total (free + target bound) serum concentrations of lunsekimig were determined using a validated ligand binding assay with a lower limit of quantification (LLOQ) of 0.0021 μg/mL. The assessed PK parameters for the SAD part included maximum serum concentration (C_{max}), time to reach C_{max} (t_{max}), area under the curve (AUC), terminal half-life ($t_{1/2z}$) for both SC and IV route of administration and concentration at the end of IV infusion [C_{eoi}], clearance (CL), and volume of distribution (V_{ss}) were specific to IV dose, whereas apparent total body clearance [CL/F], and apparent volume of distribution [V_{ss}/F] were assessed specific to SC dose. For MAD part, C_{max}, t_{max}, AUC_{tau}, $t_{1/2z}$, CL_{ss}/F, V_{ss}/F were assessed. Pharmacokinetic parameters of lunsekimig were calculated by a noncompartmental analysis using a validated software (PKDMS Version 3.2 using Phoenix 8.2 Certara™).

Pharmacodynamics

Total target concentration (free + drug-bound) of TSLP and IL-13 was measured in serum to characterize the PD effect of lunsekimig. Total target was anticipated to accumulate over time due to slower elimination of target bound to lunsekimig compared with free target elimination from serum. The accumulation of total TSLP and IL-13 levels confirms in vivo binding of lunsekimig to its respective targets. Serum samples for PD analyses were collected on Day 1 (pre-dose and 8 h post-dose for IV cohort pre-dose and 12 h for SC cohort), Day 2 (32 h for IV cohort; 24 h for SC cohort), Day 3, Day 4, Day 8, Day 15, Day 22, Day 29, Day 43, Day 57 and Day 71 (EOS) for the SAD part, and on Day 1 (pre-dose), Day 4, Day 8, Day 15 (pre-dose), Day 29 (pre-dose), Day 43, Day 50, Day 57, Day 71, Day 85, and Day 99 (EOS) for the MAD part. TSLP serum concentrations at baseline and in placebo samples were analyzed using a sensitive but nondrug-tolerant method with an LLOQ of 0.22 ng/L and a limit of detection of 0.02 ng/L. Total (free + drug-bound) TSLP serum concentrations in post-dose samples from lunsekimig-exposed participants (samples containing ≤150.0 μg/mL lunsekimig) were analyzed using a lunsekimig-tolerant method with an LLOQ of 25.00 ng/L. IL-13 serum concentrations at baseline and in placebo samples were analyzed using a sensitive but non-drug-tolerant method with an LLOQ of 0.04 ng/L and a limit of detection of 0.01 ng/L. Total (free + drug-bound) IL-13 serum concentrations in post-dose samples from lunsekimig-exposed participants (samples containing ≤50.0 μg/mL lunsekimig) were analyzed using a drug-tolerant method with an LLOQ of 5.55 ng/L. For samples containing lunsekimig ≤300.0 μg/mL, an LLOQ of 20.0 ng/L was applicable.

Immunogenicity

Antidrug antibodies (ADA) to lunsekimig were evaluated in the serum of all participants using a validated precipitation and acid dissociation immunoassay with a minimal required dilution of 50. For the SAD part, serum samples were collected at four timepoints: Day 1 (pre-dose), Day 15, Day 29, and Day 71 (EOS) and for the MAD part, serum samples were collected at five timepoints: Day 1 (pre-dose), Day 15 (pre-dose), Day 29 (pre-dose), Day 50, and Day 99 (EOS). Samples were screened for antibodies binding to lunsekimig and the titer of confirmed positive samples was reported.

Statistical analysis

Statistical analyses were performed using SAS® (SAS/Unix, Version 9.4, SAS Institute, NC, USA). Safety analyses (including AEs, laboratory parameters, vital signs, and

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ECGs) were summarized with descriptive statistics. AE severity was coded and graded according to the Medical Dictionary for Regulatory Activities (MedDRA version 25.1) and the Common Terminology Criteria for Adverse Events (CTCAE; version 5). Descriptive analyses including summary statistics were presented for PK parameters (arithmetic and geometric means, standard deviation (SD), % Coefficient of variation (CV), median, minimum, maximum) and for other quantitative variables (mean, median, SD, interquartile range, minimum, maximum) and number and percentage for categorical variables. Pharmacokinetic parameters and serum concentrations were summarized per dose level group. Dose proportionality was assessed using a power model according to the recommendations in Gough et al.[10] on C_{eoi}, AUC_{last}, and AUC for SAD and on C_{max} and $AUC_{0\text{-}tau}$ on Day 1 and Day 29 separately for MAD. For MAD, accumulation was assessed using a linear model on log-transformed accumulation ratio. Total target concentration of TSLP and IL-13, in the form of raw data and percent change from baseline were summarized as descriptive statistics. TSLP and IL-13 values below LLOQ were replaced by LLOQ/2. For immunogenicity analysis, participants were classified with preexisting ADA, treatment-induced ADA or treatment-boosted ADA and ADA incidence and titer descriptives were provided. The presence or absence of clearing ADA was explored by comparing AUC or AUC_{tau} for participants with and without ADA. Potential impact of neutralizing ADA on PD was assessed through visual inspection of individual plots of total TSLP and total IL-13 accumulation.

RESULTS

Study population

Demographic characteristics of SAD and MAD parts are presented in Table 1 and the participant disposition is summarized in Figure S2.

In the SAD part, conducted between October 2021 and June 2022, 48 participants were randomized to receive lunsekimig ($n=36$) or placebo ($n=12$) and all completed the study. The majority were white (44/48 [91.7%]) and 22/48 (45.8%) participants were male. The mean (SD) age and mean (SD) weight were 31 (6.9) years and 73.1 (12.9) kg, respectively. In the MAD part, conducted between June 2022 and December 2022, 20 participants were randomized to receive lunsekimig ($n=16$) and placebo ($n=4$) and 17 participants completed the study. The majority were white (15/20 [75%]) and 17/20 (85.0%) were male. The mean (SD) age and mean (SD) weight were 32.8 (7.2) years and 74.6 (12.7) kg respectively (Table 1). Three participants discontinued the treatment after the second dose: one in placebo group due to poor compliance to protocol, one in the lunsekimig 100 mg group due to participant withdrawal and one in the lunsekimig 200 mg group due to a TEAE of COVID-19.

Safety

An overview of the TEAE profile and most common TEAEs are presented in Table 2. All TEAEs are summarized by MedDRA preferred term in Table S1. The listing of all adverse events are outlined in Table S2.

In the SAD part, 24/36 (66.7%) participants in the lunsekimig groups and 7/12 (58.3%) participants in the placebo group experienced at least one TEAE, without any obvious dose–incidence relationship. Overall, three participants (one each from lunsekimig 90-mg IV, 200-mg IV, and 400-mg SC groups) experienced five severe TEAEs (≥Grade 3): one TEAE of COVID-19 (Grade 3) was reported in one participant in the lunsekimig 200-mg IV group and assessed as not related to lunsekimig by the investigator, and four TEAEs of increased blood creatine phosphokinase (Grade 4) were reported in two participants (one each in the lunsekimig 90-mg IV and 400-mg SC groups). The events of increased blood creatine phosphokinase were considered related to physical activity and not clinically significant by the investigator.

Treatment-emergent AESIs (all cases of COVID-19) were reported in 8/36 (22.2%) participants in the lunsekimig groups and 1/12 (8.3%) participant in the placebo group (Table 2). The most frequently reported TEAEs were COVID-19, nasopharyngitis, and headache. There were 11 injection site reactions of Grade 1 (mild) severity (erythema, discoloration, mild pain and/or itching) in 3/6 participants in the lunsekimig 400 mg SC group (Table S1).

In the MAD part, all participants in the lunsekimig 100 mg Q2W group, 7/8 (87.5%) participants in the lunsekimig 200 mg Q2W group, and 2/4 (50%) participants in the placebo group experienced at least one TEAE during the study. Three participants in lunsekimig group (two in the 100-mg Q2W group and one in the 200-mg Q2W group) reported severe TEAEs (Grade ≥3): one serious adverse event (SAE) of salivary gland adenoma was reported in one participant from the lunsekimig 100-mg group and a severe TEAE of increased blood creatine phosphokinase was reported in one participant each from the lunsekimig 100-mg SC group and the lunsekimig 200-mg group. All three events were assessed as not related to lunsekimig by the investigator. As the SAE of salivary gland adenoma occurred after the last lunsekimig administration, the participant was not discontinued from the study.

Adverse events of special interest (all cases of COVID-19) were reported in one participant in the

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TABLE 1 Participants demographic characteristics for SAD and MAD parts.

	SAD part							MAD part		
	Placebo	Lunsekimig						Placebo	Lunsekimig	
	Placebo IV/SC (*N* = 12)	10 mg IV (*N* = 6)	30 mg IV (*N* = 6)	90 mg IV (*N* = 6)	200 mg IV (*N* = 6)	400 mg IV (*N* = 6)	400 mg SC (*N* = 6)	Placebo Q2W (*N* = 4)	100 mg Q2W (*N* = 8)	200 mg Q2W (*N* = 8)
Age (years), mean (SD)	30.8 (7.3)	30.5 (6.9)	29.8 (8.7)	32.8 (5.1)	25.8 (2.4)	33.8 (8.9)	33.5 (6.3)	33.8 (5.4)	31.6 (7.7)	33.4 (8.2)
Male	5 (41.7)	1 (16.7)	2 (33.3)	4 (66.7)	4 (66.7)	4 (66.7)	2 (33.3)	4 (100)	7 (87.5)	6 (75.0)
Race, *n* (%)										
White	12 (100)	4 (66.7)	6 (100)	6 (100)	5 (83.3)	5 (83.3)	6 (100)	3 (75.0)	8 (100)	4 (50.0)
Asian	0	2 (33.3)	0	0	1 (16.7)	0	0	1 (25.0)	0	3 (37.5)
American Indian or Alaska Native	0	0	0	0	0	1 (16.7)	0	0	0	1 (12.5)
Weight (kg), Mean (SD)	71.00 (11.60)	69.67 (15.87)	80.43 (8.70)	76.73 (17.44)	72.40 (15.96)	73.95 (13.00)	69.23 (9.91)	75.78 (8.89)	75.15 (13.03)	73.34 (15.27)
BMI (kg/m^2)	24.04 (2.30)	24.48 (3.81)	26.07 (2.38)	25.32 (3.75)	23.67 (3.00)	24.13 (3.28)	23.65 (1.96)	24.43 (2.83)	24.28 (2.83)	24.73 (3.58)

Note: Q2W, corresponds to administration on Day 1, 15 and 29 respectively.

Abbreviations: BMI, body mass index; IV, intravenous; MAD, multiple ascending dose; Q2W, every 2 weeks; SAD, single ascending dose; SC, Subcutaneous; SD, standard deviation.

lunsekimig 100-mg Q2W group and two participants in the lunsekimig 200-mg Q2W group (Table 2). Injection site reactions were the most common TEAEs. All were of Grade 1 (mild) severity and resolved fully without any corrective treatment (Table S1).

In both SAD and MAD parts, no clinically relevant abnormalities were found in vital signs, ECGs, or laboratory parameters. Blockade of IL-13 may be associated with an increase in blood eosinophil counts, whereas blockade of TSLP may be associated with a decrease in blood eosinophil counts. Overall, there was no clinically relevant increase in mean eosinophil counts in the lunsekimig groups across SAD and MAD parts (Figure S3).

Pharmacokinetics

Single ascending dose part

Serum concentration by time profiles of single IV infusion (10–400 mg) and a single SC administration (400 mg) of lunsekimig are presented in Figure 2a,b. Following a single 1 h IV infusion, median t_{max} was between 2.51 and 4.04 h after the start of infusion. Linear elimination was observed following an initial distribution phase at all dose levels. Following single SC administration, median t_{max} was around 4.5 days postdosing (Table 3). The comparison of mean lunsekimig serum concentration–time profiles after lunsekimig 400 mg SC versus IV administration is presented in Figure S4. The absolute bioavailability of lunsekimig after a single SC administration of 400 mg was 54%.

The mean $t_{1/2z}$ of lunsekimig was around 10 days across IV and SC doses. Mean clearance of lunsekimig was constant across IV doses, ranging from 0.0130 to 0.0147 L/h (Table 3).

Dose proportionality assessment of lunsekimig after a single IV infusion is presented in Table S3. C_{eoi} and AUCs increased proportionally with the dose ranging from 10 to 400 mg. Overall, C_{eoi} and AUCs increased linearly with dose from 10 to 400 mg, assessed using the power model [C_{eoi}, 34.79-fold (90% confidence interval [CI]: 29.06–41.65) and AUC 36.57-fold (90% CI: 28.44–47.02)].

Multiple ascending dose part

Serum PK parameters following the first (Day 1) and the third (Day 29) SC administration of 100 and 200 mg lunsekimig Q2W are summarized in Table 4. Mean serum concentration by time profiles after the first and last dose are shown in Figure 2c,d.

After the first SC administration of 100 or 200 mg, median t_{max} for lunsekimig was observed 3- or 7-days

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TABLE 2 Overview of adverse event profile (safety population).

	SAD part							MAD part		
	Placebo	Lunsekimig						Placebo	Lunsekimig	
n (%)	IV/SC (*N* = 12)	10 mg IV (*N* = 6)	30 mg IV (*N* = 6)	90 mg IV (*N* = 6)	200 mg IV (*N* = 6)	400 mg IV (*N* = 6)	400 mg SC (*N* = 6)	Q2W SC (*N* = 4)	100 mg Q2W SC (*N* = 8)	200 mg Q2W SC (*N* = 8)
Participants with any TEAE	7 (58.3)	3 (50.0)	3 (50.0)	3 (50.0)	5 (83.3)	5 (83.3)	5 (83.3)	2 (50.0)	8 (100)	7 (87.5)
Participants with any grade ≥3 TEAE	0	0	0	1 (16.7)	1 (16.7)	0	1 (16.7)	0	2 (25.0)	1 (12.5)
Participants with any treatment-emergent SAE[a]	0	0	0	0	0	0	0	0	1 (12.5)	0
Participants with any TEAE leading to permanent study intervention discontinuation[b]	0	0	0	0	0	0	0	0	0	1 (12.5)
Participants with any treatment-emergent AESI[c]	1 (8.3)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	3 (50.0)	0	0	1 (12.5)	2 (25.0)
Most common TEAEs (observed in at least 20% of participants in at least one treatment group)										
Nasopharyngitis	3 (25.0)	1 (16.7)	0	0	2 (33.3)	0	1 (16.7)	1 (25.0)	3 (37.5)	1 (12.5)
COVID-19	1 (8.3)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	3 (50.0)	0	0	1 (12.5)	2 (25.0)
Influenza	0	0	0	0	0	0	0	1 (25.0)	0	0
Rhinitis	0	0	0	0	0	0	0	1 (25.0)	0	0
Headache	1 (8.3)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (16.7)	0	1 (12.5)	2 (25.0)
Cough	0	0	0	0	0	1 (16.7)	2 (33.3)	0	0	0
Injection site reaction	0	0	0	0	0	0	3 (50.0)	0	6 (75.0)	5 (62.5)

Note: *n* (%), number and percentage of participants with at least one TEAE.

Abbreviations: AESI, adverse event of special interest; IV, intravenous; MAD, multiple ascending dose; Q2W, every 2 weeks; SC, subcutaneous; SAD, single ascending dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]One participant in the lunsekimig 100 mg Q2W group reported a salivary gland adenoma as treatment-emergent SAE.

[b]One participant in the lunsekimig 200 mg Q2W group reported COVID-19 leading to permanent study discontinuation as per study stopping rules.

[c]All cases of COVID-19.

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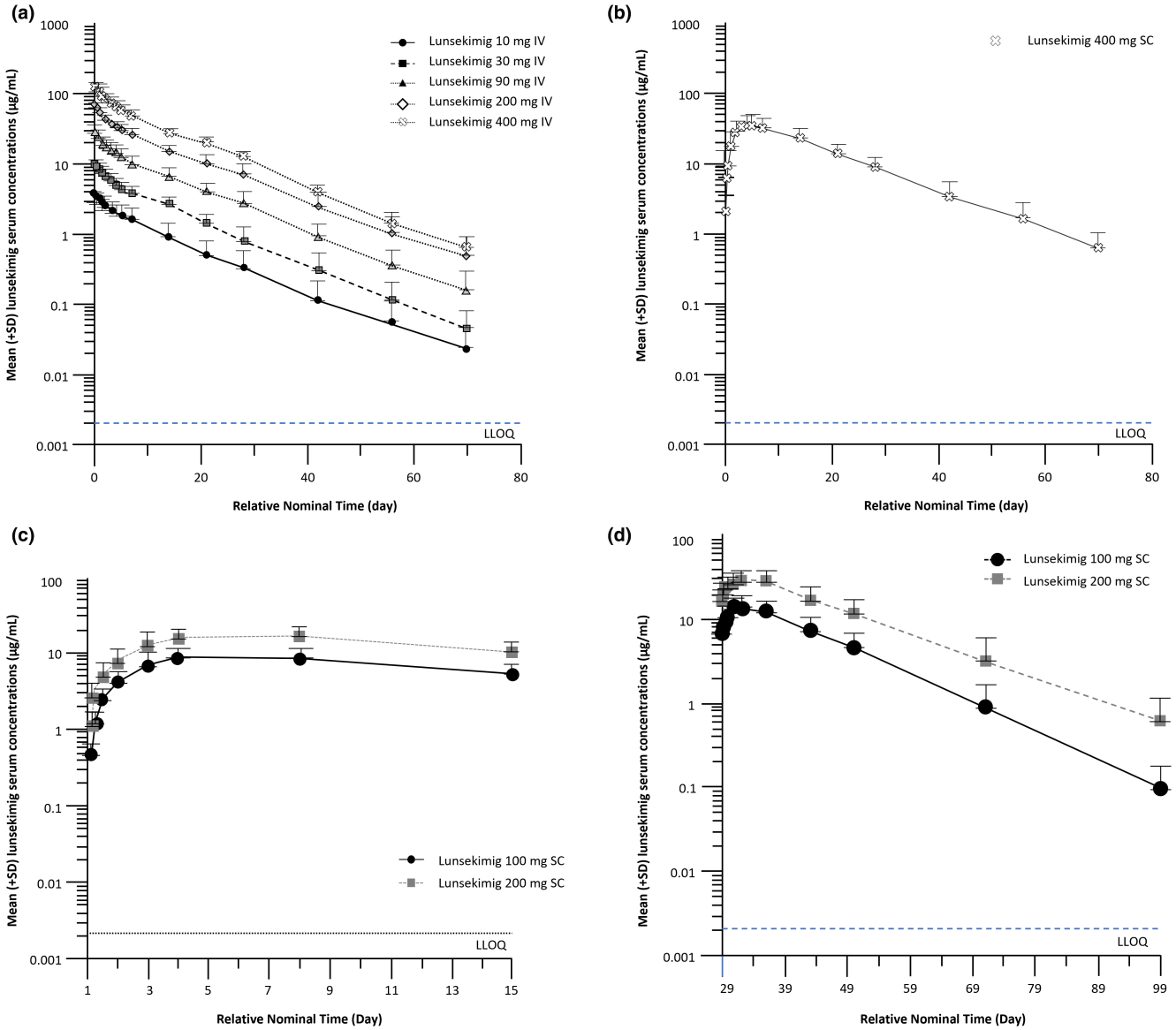

FIGURE 2 Mean (±SD) lunsekimig serum concentration by time profiles after (a) single IV infusion (10–400 mg) and (b) single SC administration (400 mg) of lunsekimig from SAD part or after (c) the first SC administration (Day 1) and (d) the third administration (Day 29) of 100 to 200 mg of lunsekimig Q2W from MAD part. IV, intravenous; MAD, multiple ascending dose; Q2W, every 2 weeks; SAD, single ascending dose; SC, subcutaneous.

post-dose, respectively, and 2- or 3-days post-dose after the third administration, respectively.

The mean $t_{1/2z}$ was estimated as 8.5 days and as 10 days for lunsekimig 100 and 200 mg, respectively. Dose proportionality assessment for lunsekimig on C_{max} and $AUC_{0\text{-}tau}$ at Day 1 and Day 29 is presented in Table S4. Using the power model, for a twofold increase in dose from 100 mg to 200 mg, after the first administration, C_{max} and $AUC_{0\text{–}tau}$ increased on average by 1.77-fold (90% CI: 1.27–2.47) and 1.85-fold (90% CI: 1.33–2.58), respectively, and after the third administration, C_{max} and $AUC_{0\text{–}tau}$ increased on average by 2.05-fold (90% CI: 1.37–3.09) and 2.18-fold (90% CI: 1.46–3.25), respectively.

Steady state was not reached after the third administration. Observed accumulation ratios for C_{max} and $AUC_{0\text{–}tau}$ are presented in Table S5. Accumulation did not appear to be dose-dependent. The accumulation ratio estimate of pooled doses for C_{max} was 1.66 (90% CI: 1.52–1.82) and for $AUC_{0\text{–}tau}$ was 1.82 (90% CI: 1.68–1.97).

Pharmacodynamics

Baseline concentrations of TSLP were comparable in all treatment groups with mean ± SD values ranging from 0.219 ± 0.076 to 0.366 ± 0.205 ng/L in SAD part

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TABLE 3 Serum pharmacokinetic parameters of lunsekimig, following a single IV infusion of 10 to 400 mg or a single SC administration of 400 mg of lunsekimig (SAD part).

	Serum Lunsekimig Pharmacokinetics					
Parameters	**10 mg IV (*N* = 6)**	**30 mg IV (*N* = 6)**	**90 mg IV (*N* = 6)**	**200 mg IV (*N* = 6)**	**400 mg IV (*N* = 6)**	**400 mg SC (*N* = 6)**
C_{eoi}[a] (μg/mL)	3.66 ± 0.915 (3.57) [25.0]	9.25 ± 1.76 (9.11) [19.0]	28.7 ± 8.25 (27.8) [29.0]	66.9 ± 9.81 (66.3) [15.0]	117 ± 23.9 (115) [20.0]	NA
C_{max} (μg/mL)	3.87 ± 0.788 (3.81) [20.0]	9.44 ± 1.61 (9.32) [17.0]	28.9 ± 8.05 (28.1) [28.0]	71.9 ± 8.48 (71.5) [12.0]	123 ± 19.1 (122) [16.0]	36.2 ± 14.7 (33.7) [41.0]
t_{max} (h)	2.51 (1.00–4.00)	2.51 (1.00–4.22)	2.57 (1.00–4.02)	2.53 (1.00–4.15)	4.04 (1.00–8.00)	107 (96.0–168)
AUC (μg*h/mL)	908 ± 439 (831) [48.0]	2220 ± 670 (2140) [30.0]	6560 ± 1970 (6350) [30.0]	15,800 ± 3340 (15500) [21.0]	29,100 ± 5100 (28700) [18.0]	17,900 ± 7280 (16800) [41.0]
$t_{1/2z}$ (Day)	9.93 ± 2.29 (9.70) [23.0]	9.42 ± 1.96 (9.22) [21.0]	9.91 ± 1.86 (9.77) [19.0]	10.5 ± 1.77 (10.4) [17.0]	9.72 ± 0.874 (9.68) [9.00]	10.8 ± 1.53 (10.7) [14.0]
CL (L/h)	0.0130 ± 0.00547 (0.0120) [42.0]	0.0147 ± 0.00485 (0.0140) [33.0]	0.0146 ± 0.00367 (0.0142) [25.0]	0.0131 ± 0.00259 (0.0129) [20.0]	0.0141 ± 0.00216 (0.0139) [15.0]	NA
V_{ss} (L)	3.54 ± 0.759 (3.47) [21.0]	3.92 ± 0.507 (3.90) [13.0]	4.61 ± 0.933 (4.52) [20.0]	4.30 ± 0.393 (4.28) [9.00]	4.43 ± 0.673 (4.39) [15.0]	NA
CL/F (L/h)	NA	NA	NA	NA	NA	0.0250 ± 0.00810 (0.0237) [32.0]
V_{ss}/F (L)	NA	NA	NA	NA	NA	10.4 ± 3.82 (9.78) [37.0]

Note: Values are presented as mean ± SD (geometric mean) [CV%], except for t_{max}, which is shown as median [min–max].

Abbreviations: AUC, area under the curve; C_{eoi}, concentration at the end of IV infusion; CL, clearance; CL/F, apparent total body clearance; C_{max}, maximum serum concentration; CV, coefficient of variation; IV, intravenous; NA, not applicable; SAD, single ascending dose; SC, subcutaneous; SD, standard deviation; $t_{1/2z}$, terminal half-life; t_{max}, time to reach C_{max}; V_{ss}, volume of distribution; V_{ss}/F, apparent volume of distribution.

[a]Mean infusion duration of approximately 1 h for all IV doses.

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TABLE 4 Pharmacokinetic parameters after the first SC administration of 100 to 200 mg of lunsekimig Q2W in the MAD part by dose and treatment day.

	Day 1	
	Lunsekimig 100 mg (*N* = 8)	**Lunsekimig 200 mg (*N* = 8)**
C_{max} (μg/mL)	9.05 ± 2.59 (8.63) [29.0]	16.4 ± 6.46 (15.3) [39.0]
t_{max} (h)	72.00 [72.00–169.87]	166.27 [69.17–169.78]
AUC_{tau} [a] (h*ng/mL)	2290 ± 647 (2190) [28.0]	4350 ± 1780 (4060) [41.0]
	Day 29	
	Lunsekimig 100 mg (*N* = 7)	**Lunsekimig 200 mg (*N* = 7)**
C_{max} (μg/mL)	14.3 ± 4.39 (13.5) [31.0]	30.3 ± 13.3 (27.8) [44.0]
t_{max} (h)	48.02 [48.00–170.03]	72.00 [24.00–167.78]
AUC_{tau} (h*ng/mL)	3780 ± 1190 (3590) [32.0]	8570 ± 3840 (7830) [45.0]
$t_{1/2z}$ (Day)	8.52 ± 1.57 (8.39) [18.0]	10.1 ± 3.11 (9.49) [31.0]
CL_{ss}/F [b] (L/h)	0.0297 ± 0.0128 (0.0279) [43.0]	0.0280 ± 0.0130 (0.0256) [46.0]
Vss/F [b] (L)	11.7 ± 4.16 (11.2) [36.0]	12.1 ± 5.19 (11.2) [43.0]

Note: Values are mean ± SD (geometric mean) [CV%] except for t_{max} which is shown as median [min–max].

Abbreviations: AUC, area under the curve; C_{max}, maximum serum concentration; CL/F, apparent total body clearance; CV; MAD, multiple ascending doses; Q2W, every 2 weeks, SC, subcutaneous; SD, standard deviation; $t_{1/2z}$, terminal half-life; t_{max}, time to reach C_{max}; V_{ss}, volume of distribution; V_{ss}/F, apparent volume of distribution.

[a] AUC_{tau} is $AUC_{0\text{-}336h}$.

[b] CL_{ss}/F and V_{ss}/F have been reported even though steady state was not reached.

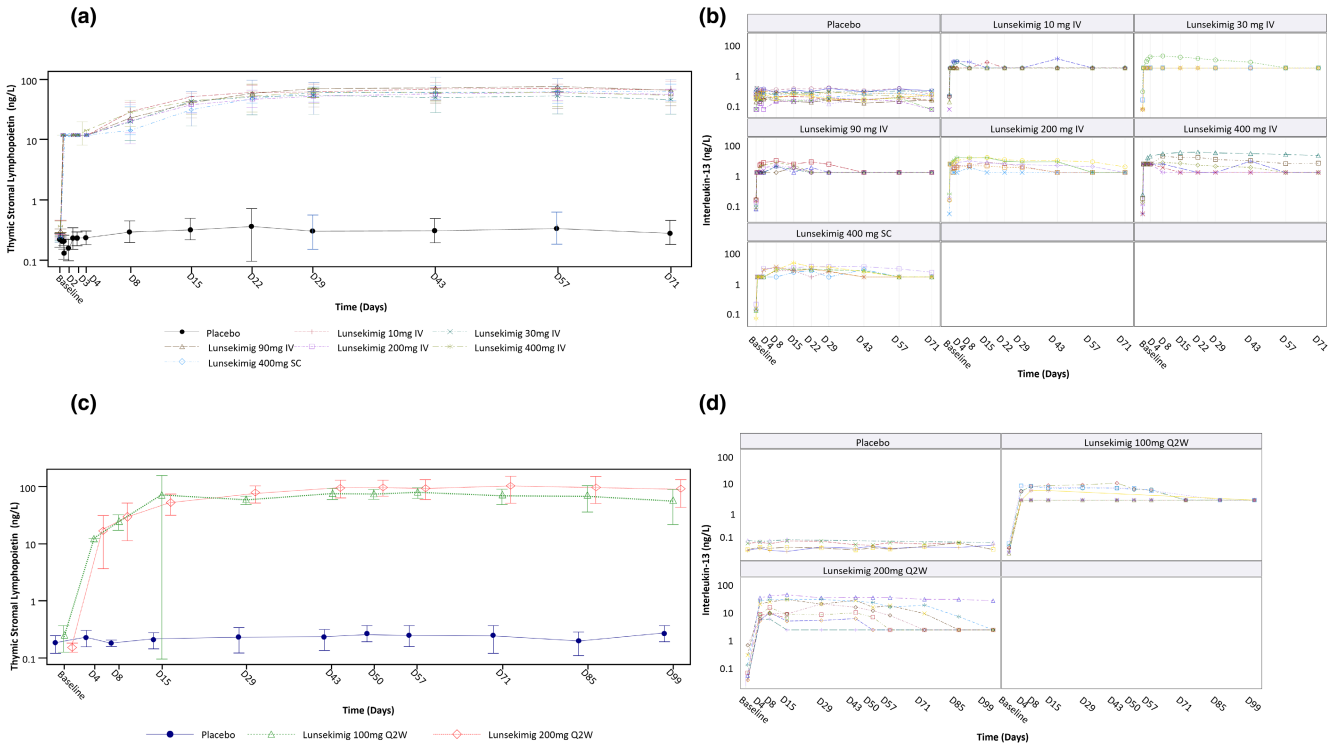

FIGURE 3 Total target concentration–time profile semi-log plots of (a) TSLP of SAD part, (b) IL-13 of SAD part (individual), (c) TSLP of MAD part, and (d) IL-13 of MAD part (individual). 100 mg/200 mg Q2W corresponds to 100/200 mg administration (on Day 1, 15 and 29). D, day; IL, interleukin; IV, intravenous; MAD, multiple ascending doses; Q2W, twice in a week; SAD, single ascending dose; SC, subcutaneous; TSLP, thymic stromal lymphopoietin.

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TABLE 5 Summary of ADA incidence for SAD and MAD parts of the study.

	SAD part							MAD part		
	Placebo	Lunsekimig						Placebo	Lunsekimig	
	IV/SC ($N=12$)	10 mg IV ($N=6$)	30 mg IV ($N=6$)	90 mg IV ($N=6$)	200 mg IV ($N=6$)	400 mg IV ($N=6$)	400 mg SC ($N=6$)	Q2W SC ($N=4$)	100 mg Q2W SC ($N=8$)	200 mg Q2W SC ($N=8$)
Participants with ADA negative, *n/N*	10/12	5/6	5/6	5/6	6/6	6/6	6/6	4/4	7/8	8/8
Participants with treatment-induced ADA, *n/N*	1/10	0/5	1/5	1/5	0/6	1/6	1/6	0/4	3/7	4/8
Median peak titer (1/dilution), Min; Max peak titer	50[a]	–	50[a]	50[a]	–	50[a]	50[a]	–	50 50; 200	75 50; 1600
Participants with ADA-positive at baseline, *n/N*	2/12	1/6	1/6	1/6	0/6	0/6	0/6	0/4	1/8	0/8
Participants with treatment-boosted ADA, *n/N*	0/2	0/1	0/1	0/1	–	–	–	–	0/1	–
Participants with treatment-emergent ADA (incidence), *n/N*	1/12	0/6	1/6	1/6	0/6	1/6	1/6	0/4	3/8	4/8
Participants without treatment-emergent ADA, *n/N*	11/12	6/6	5/6	5/6	6/6	5/6	5/6	4/4	5/8	4/8
ADA-inconclusive participants, *n/N*	0/12	0/6	0/6	0/6	0/6	0/6	0/6	0/4	0/8	0/8

Note: 100 mg/200 mg Q2W corresponds to 100/200 mg administration (on Day 1, 15, and 29, respectively).

Abbreviations: ADA, antidrug antibody; IV, intravenous; MAD, multiple ascending doses; Q2W, every 2 weeks; SAD, single ascending dose; SC, subcutaneous.

[a]Data presented with only median peak titers as data were from only one participant.

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and from 0.163 ± 0.027 to 0.246 ± 0.118 ng/L in MAD part. Following lunsekimig administration, total (free + drug-bound) TSLP concentrations increased to a plateau in all lunsekimig groups, indicative of target engagement, without a clear dose–response relationship (Figure 3a,c).

The mean ± SD baseline IL-13 concentrations ranged from 0.021 ± 0.013 to 0.052 ± 0.036 ng/L across all treatment groups in the SAD part. In the MAD part, baseline IL-13 varied with mean ± SD concentrations of 0.056 ± 0.024 ng/L for the placebo group, 0.042 ± 0.013 ng/L for the lunsekimig 100-mg group, and 0.193 ± 0.258 ng/L for the lunsekimig 200-mg group. In the SAD part, total (free + drug-unbound) IL-13 concentrations were below the LLOQ for 66% of on-treatment samples. Out of 36 participants, 27 had at least one post-dose sample with an IL-13 concentration above the LLOQ, confirming target engagement for IL-13. These individual profiles are shown in Figure 3b. Following lunsekimig administration in the MAD part, total IL-13 concentrations were below the LLOQ of 5.55 ng/L for 50% of on-treatment samples for the lunsekimig groups. Out of 16 participants, 12 had at least one post-dose sample with an IL-13 concentration above this LLOQ, confirming target engagement for IL-13. These individual profiles are shown in Figure 3d. The seemingly dose-related trend in accumulation was driven by a higher baseline for the 200-mg group as the relative change from baseline was similar in both dose groups (data not shown).

Immunogenicity

Out of 36, 4 (11.1%) participants who received a single dose of lunsekimig in the SAD part developed treatment-emergent ADAs, with no apparent dose dependency. Three participants in the treatment group had preexisting ADAs, but none had a treatment-boosted response. Treatment-induced ADA titers were low (≤50) (Table 5).

Out of 16, 7 (43.8%) participants who received lunsekimig in the MAD part developed treatment-emergent ADAs. Preexisting ADAs were detected in one participant, and this response was not treatment boosted. Overall, treatment-emergent ADAs from six of the seven ADA-positive participants were generally observed after the first dose and persisted at low titers until EOS, except for one participant in the 200-mg group that had an ADA titer of 1600 after the third dose (Table 5). Based on a preliminary assessment, there was no apparent impact of ADAs on safety, PK, or PD across both study parts (Figures S5 and S6).

DISCUSSION

This is the first report of lunsekimig, a novel biologic targeting both TSLP and IL-13, administered to humans. In this first-in-human study, single IV doses up to 400 mg, a single SC dose of 400 mg and multiple SC doses (Q2W for three doses) up to 200 mg of lunsekimig were well tolerated in healthy adult participants, with dose-proportional increase in exposure, linear elimination and confirmed target engagement for both TSLP and IL-13.

Lunsekimig is a bispecific NANOBODY® compound. As a NANOBODY® molecule, lunsekimig lacks the Fc portion common to conventional mAbs, eliminating risks associated to Fc-mediated effector functions, such as complement activation or phagocytic clearance.[11,12] In addition, due to their small size and unique structure, multiple NANOBODY® building blocks can be combined to engage multiple targets in a single drug molecule in a "mix and match" form.[13] By simultaneously blocking both TSLP and IL-13, two clinically validated targets in the field of immune-inflammation, lunsekimig may potentially lead to additive and/or synergistic benefits in immune-mediated diseases such as asthma.

In this study on healthy adult participants, the combined TSLP/IL-13 blockade was well tolerated, which is consistent with previous reports for monospecific anti-TSLP and anti-IL-13 mAbs blocking single targets.[3–6,14] No safety signal was observed based on the AE profile, vital signs, ECGs or laboratory parameters and no increase in eosinophil levels was observed. No lunsekimig-related SAEs were reported. Subcutaneous administration of lunsekimig appeared to be associated with increased occurrence of injection site reactions with no clear dose relationship. Injection site reactions were mainly mild and self-limiting, without the need for corrective treatment. It should be noted that all injection site reactions were recorded as TEAE, regardless of their clinical significance of CTCAE grading. A similar safety profile was observed in Part 2 of this study in participants with mild-to-moderate asthma, for which the results will be published separately.[9]

In the investigated dose range, exposure increased dose-proportionally after single IV infusion as well as following multiple SC dosing after the first and third administration. After single and repeated SC administration of lunsekimig, median t_{max} in healthy participants ranged from 2 to 7 days postdosing. The absolute bioavailability (AUC_{SC}/AUC_{IV}) of lunsekimig after a single SC administration of 400 mg in healthy participants was 54%. A biphasic PK profile was observed after single IV infusion, with linear elimination following an initial distribution phase. Based on the rather small volume of distribution, lunsekimig is expected to be largely confined to the systemic circulation and well-perfused organs. The $t_{1/2z}$ was

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similar across dose groups, approximately 10–11 days. Steady state was not reached after the third administration following Q2W SC dosing and the respective accumulation was in line with the observed $t_{1/2z}$. The variability in lunsekimig exposure was low to moderate across dose levels and repeated administrations.

Target engagement for TSLP and IL-13 was demonstrated by an increase of total (free + drug-bound) target serum concentrations. The increased total target concentrations are explained by a prolonged $t_{1/2}$ due to binding of the target to lunsekimig and nearly completely constitute of complexes with lunsekimig, which are expected to be biologically inactive. Because of insufficient sensitivity of the post-dose assay, only partial data could be obtained for IL-13, which still confirmed target engagement in most participants. The observed total target data were too limited to clearly display a dose–response relationship in the current study, given inter-individual variability in baseline levels and accumulation, together with limited assay sensitivity to well capture the terminal phase. Nevertheless, the data could be leveraged to predict free IL-13 and TSLP target levels over time after administration of lunsekimig, in a dynamic environment with changing drug and drug–target complex concentrations, and continuous target production.

Antibodies to lunsekimig were detected with a higher incidence in MAD cohorts (43.8%) compared with SAD cohorts (11.1%). However, treatment-induced ADA generally appeared after the first dose and persisted at low titers with the vast majority of titers below 200. Of note, a similar incidence of 13.6% of treatment-induced ADA with low titers (≤100) was observed in participants with mild-to-moderate asthma after a single administration of 400 mg lunsekimig (unpublished data). No ADA-related TEAE was observed. Based on a preliminary assessment, no noticeable impact of ADAs on PK or PD (total TSLP and IL-13 concentrations) was observed, indicating the absence of clearing and/or neutralizing potential. The immunogenicity of lunsekimig after long-term treatment is currently being assessed in the phase IIb dose ranging study AIRCULES (NCT06102005).

In conclusion, lunsekimig, a novel bispecific anti-TSLP/anti-IL-13 NANOBODY® molecule, was well tolerated in healthy adult participants up to a single 400 mg IV and SC doses and multiple doses of 100 and 200 mg SC Q2W, with no clinically meaningful immunogenicity. Moreover, lunsekimig exhibited a linear PK profile, and accumulation of total target levels confirmed target engagement for both TSLP and IL-13. The findings of this study support the further clinical development of lunsekimig for the treatment of asthma and potentially other Type 2 inflammatory conditions. The efficacy, safety, and tolerability of add-on therapy with lunsekimig in adults with moderate-to-severe asthma are currently being assessed in the phase IIb dose ranging study AIRCULES (NCT06102005).

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. A.D., L.B., N.D., B.S., H.S., and E.K. designed the research. A.D. and S.B. performed the research. A.D., L.B., G.C., M.V., and M.G. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

Annemie Deiteren, Lieselot Bontinck, Griet Conickx, Nele Dervaux, Matthieu Gassiot, Benjamin Suratt, Heribert Staudinger, Emmanuel Krupka are Sanofi employees and may hold stock and/or stock options in the company. Marie Vigan is an employee of Ividata Life Sciences (contracted by Sanofi). Selcuk Bas declared no competing interests for this work.

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SUPPORTING INFORMATION

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

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