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ARTICLE

Pharmacokinetics and pharmacodynamics of itepekimab in healthy adults and patients with asthma: Phase I first-in-human and first-in-patient trials

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Abstract

Itepekimab is a monoclonal antibody that targets interleukin (IL-33) and has been shown to reduce airway inflammation and associated tissue damage in preclinical studies. We assessed the safety, tolerability, pharmacokinetics (PKs), and pharmacodynamic profiles of single-ascending and multiple-ascending doses of itepekimab in two randomized, double-blind, placebo-controlled phase I studies. Healthy adults ($N = 40$) were randomized to the single-dose study and patients with moderate asthma ($N = 23$) to the multiple-dose study. Itepekimab was administered intravenously (0.3, 1, 3, or 10 mg/kg infusion) or subcutaneously (150 mg) in the single-dose study and subcutaneously (75 or 150 mg weekly for 4 weeks) in the multiple-dose study. Itepekimab exhibited linear PKs across studies and dose-proportional increases in mean maximum concentration in serum and area under the concentration–time curve following single intravenous or multiple subcutaneous doses. Itepekimab demonstrated mean subcutaneous bioavailability of 59–73% and a long terminal half-life (30.0–31.6 days). IL-33 concentrations in most healthy participants and patients with asthma were undetectable at baseline. Following administration of itepekimab in both studies, total IL-33 concentrations increased and blood eosinophils decreased, both with durable effect. Itepekimab was well-tolerated in both studies with no detection of treatment-emergent anti-drug antibody responses.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Preclinical data suggest that itepekimab, a monoclonal antibody targeting IL-33, may benefit patients with chronic inflammatory airway diseases by blocking IL-33–mediated pathologic inflammation. Neither the pharmacokinetic (PK) profile of itepekimab nor its safety has been fully elucidated in first-in-human or first-in-patient studies.

WHAT QUESTION DID THIS STUDY ADDRESS?
The study evaluated the initial safety of itepekimab, and its PK and pharmacodynamic activity in healthy adults and patients with asthma.
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Itepekimab demonstrated linear and dose-proportional PKs in our studies and was well-tolerated, with no evidence of immunogenicity. These findings have facilitated dose and regimen selection for subsequent clinical studies in patients with asthma and chronic obstructive pulmonary disease.
HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
Itepekimab is one of a few anti-alarmin biologics under development; if successful, it may provide an alternative mechanism of action with which to target chronic inflammatory airway diseases, alone or in combination with other targeted therapies.

INTRODUCTION

Globally, an estimated 545 million people suffer from chronic respiratory diseases, which cause significant morbidity and mortality.[1,2] Of these, chronic obstructive pulmonary disease (COPD) and asthma are the most common conditions, with a recent estimated prevalence of 3.9% and 3.6%, respectively.[2] Asthma and COPD are characterized by airway inflammation due to inhaled triggers, leading to disease exacerbations and reduced lung function.[3–5] Blockade of type 2 immune response pathways with monoclonal antibodies (mAbs) targeting IgE,[6] interleukin (IL)-4/13,[7–9] and IL-5[10–13] have improved clinical outcomes in certain subsets of patients with asthma that is uncontrolled despite the use of inhaled corticosteroids (ICS). Biologics blocking IL-5 signaling have demonstrated mixed results in COPD,[14–16] and none have been approved by the US Food and Drug Administration to treat COPD.[17] Despite the availability of inhaled treatments, and, in some cases, effective biologics, significant chronic respiratory disease burden still exists,[17–19] highlighting the need to target alternative immune signaling pathways to treat asthma and COPD.

IL-33 is an alarmin released by damaged airway epithelial and endothelial cells in response to cell stress or damage caused by exposure to airborne allergens, viruses, cigarette smoke, and air pollutants.[20,21] The binding of IL-33 to the ST2 receptor expressed on immune cells recruits the IL-1 receptor accessory protein (IL-1RAcP) and activates the nuclear factor (NF)-kB and mitogen-activated protein kinase (MAPK) signaling pathways. These pathways lead to the release of proinflammatory cytokines that initiate and amplify innate and adaptive inflammatory cascades.[21] The relative contribution of IL-33 and other epithelial-derived alarmins, such as IL-25 and thymic stromal lymphopoietin, as well as alarmin redundancy in chronic inflammation in respiratory diseases, such as asthma and COPD, is under active investigation.[22]

Itepekimab, formerly known as REGN3500 and SAR440340, is a human $IgG4^P$ mAb against IL-33, produced using VelocImmune® technology involving a proprietary mouse model with an optimally, genetically humanized immune system.[23,24] $IgG4^P$ antibodies readily form dimers due to a serine to proline substitution in the hinge region of the IgG4 constant domain.[25] A preclinical study using the house dust mite (HDM) lung inflammation model demonstrated that itepekimab-mediated IL-33 blockade reduced airway inflammation and tissue damage in mice,[26] providing evidence that itepekimab may inhibit inflammatory cascades that contribute to respiratory diseases with epithelial dysfunction. The ongoing phase III AERIFY-1 (NCT04701983) and AERIFY-2 (NCT04751487) trials are assessing the safety and efficacy of itepekimab in patients with COPD.

We report the results from two randomized, double-blind, placebo-controlled, phase I itepekimab clinical studies: an intravenous (i.v.) or subcutaneous (s.c.) single ascending-dose, first-in-human study in healthy participants (R3500-HV-1551) and an s.c., multiple ascending-dose, first-in-patient study in patients with moderate asthma (R3500-AS-1619). The aims of the studies were to assess the safety, tolerability, pharmacokinetics (PKs), and pharmacodynamics (PDs) of itepekimab in healthy adults and patients with moderate asthma.

METHODS

Study designs and participants

Both studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International

Council for Harmonization Guideline for Good Clinical Practice and applicable regulatory requirements. Informed consent was obtained from each patient participating in the study prior to initiating the study. Protocols and informed consent forms were approved by relevant institutional review boards or ethics committees. Patients, principal investigators, and study site personnel were blinded to all randomization assignments throughout the study.

Single ascending-dose study

The single ascending-dose study (R3500-HV-1551, NCT02958436) assessed the safety, tolerability, and PKs of i.v. or s.c. administered itepekimab in healthy adults. Participants were randomized 3:1 to receive itepekimab or placebo within 5 cohorts: 0.3, 1, 3, or 10 mg/kg by i.v. infusion over the course of greater than or equal to 1 h; or 150 mg by s.c. injection. Doses were selected based on preclinical safety and pharmacology data. Eight participants were included per cohort, of whom two received placebo. The i.v. cohorts were enrolled sequentially, with enrollment opened to the next higher dose after the last participant in the previous lower dose cohort was monitored for safety and tolerability for at least 7 days; the 150 mg s.c. and 3 mg/kg i.v. cohorts were enrolled in parallel. Dose escalation decisions according to predefined stopping rules were made following blinded safety review.

The study consisted of a screening period (day −28 to day −2); a pre-baseline visit (day −1) during which participants were admitted to the clinic for either a 48-h clinic stay (i.v. dosing) or a 32-h clinic stay (s.c. dosing); and a follow-up period including an end of study visit (day 4–day 113 for the 0.3 mg/kg i.v. dose, day 4–day 203 for the 1 mg/kg and 3 mg/kg i.v. doses and 150 mg s.c. dose, and day 4–day 293 for the 10 mg/kg i.v. dose). Due to the long terminal half-life ($t_{1/2}$) of itepekimab observed in the initial 0.3 mg/kg cohort, the duration of PK sampling was extended to day 203 (1 mg/kg i.v., 3 mg/kg i.v., and 150 mg s.c. doses) or day 293 (10 mg/kg i.v. dose) to ensure adequate characterization of the concentration–time profiles. The single-dose study was conducted at one site in Europe.

Healthy adult men and women aged 18–65 years with no history of asthma, COPD, or lung diseases requiring the use of chronic controllers were eligible for enrollment. Additional key inclusion criteria were a body mass index of less than or equal to 33 kg/m^2 and good health according to medical history, physical examination, vital signs, laboratory safety tests, electrocardiogram (ECG), and blood pressure readings. Full eligibility criteria are listed in the Supplementary Information.

Multiple ascending-dose study

The multiple ascending-dose study (R3500-AS-1619, NCT02999711) evaluated the safety, tolerability, PKs, and PDs of repeat s.c.-administered itepekimab in adult patients with moderate asthma. Patients were randomized 3:1 to two sequential ascending s.c. dose cohorts: itepekimab 75 mg s.c. (6 patients) or placebo s.c. (2 patients) once weekly (q.w.) for a total of four doses or itepekimab 150 mg s.c. (11 patients) or placebo s.c. (4 patients) q.w. for a total of four doses. Safety and tolerability of itepekimab were established in the 75 mg s.c. dose cohort prior to enrolling the 150 mg s.c. cohort. Itepekimab dosing was governed by predefined stopping rules, in which individual patient dosing was stopped if a patient experienced a serious adverse event (AE) considered related or possibly related to itepekimab, or had a severe AE related or possibly related to itepekimab that jeopardized the patient's safety. The study would have been halted if one serious AE or greater than or equal to two severe AEs related to or possibly related to itepekimab occurred.

The study consisted of a screening period (day −28 to day −1 with an in-clinic visit performed between day −28 and day −14); a baseline visit (day 1); a treatment period (day 1–day 22); and a follow-up period including an end of study visit (day 29–day 250). The total planned duration of a patient's participation in the study was ~ 40 weeks (including the screening period of up to 4 weeks). The study was conducted at three sites in the United Kingdom.

The enrolled patients included adults aged 18–60 years with a diagnosis of moderate asthma (for a period of ≥2 years prior to screening), who were using a stable, medium daily dose of ICS as defined by GINA guidelines (total daily dose of ICS >400 μg to ≤800 μg/day of budesonide or equivalent for ≥1 month prior to screening and during the study).[27] Other key inclusion criteria included a pre-bronchodilator forced expiratory volume in 1 ml reversibility greater than or equal to 12% or greater than or equal to 200$_1$) percentage predicted between 60% and 90%, and FEV$_1$s (FEV over baseline after 400 μg salbutamol pressurized metered-dose inhalation. Full eligibility criteria are listed in the Supplementary Information.

Outcomes

The primary end points of both studies were the incidence and severity of treatment-emergent adverse events (TEAEs) in participants treated with itepekimab. Additional end points included the PK parameters describing the serum concentration–time profile of itepekimab, the concentrations of total IL-33 and total soluble ST2 (sST2) in serum and of eosinophils in blood, and detection of anti-drug antibody (ADA) responses.

Study assessments

Blood samples for measuring functional itepekimab, total IL-33, and total sST2 were collected in both studies. Functional itepekimab (i.e., itepekimab with ≥1 unoccupied binding site) concentrations in serum were measured using a validated enzyme-linked immunosorbent assay (ELISA) on serum samples taken prior to each dose (lower limit of quantification [LLOQ] = 0.078 mg/L), and at prespecified intervals up to days 113–293 in the single-dose study (varied by cohort) or up to day 250 (in the multiple-dose study). The functional itepekimab PK assay utilized itepekimab as the assay standard and human IL-33 as the capture reagent. The concentration of total IL-33, which includes both free IL-33 and IL-33 bound to itepekimab or sST2, was determined from serum samples using an electrochemiluminescence immunoassay (LLOQ = 31.3 pg/ml). The assay included acid pretreatment of serum samples to improve detection of IL-33 in the presence of itepekimab or sST2. Total IL-33 was captured by a biotinylated anti–IL-33 human mAb and detected by a ruthenylated anti-human IL-33 mAb. The concentration of total sST2 in human serum, specifically for the dominant free sST2, was determined by ELISA (LLOQ = 625 pg/ml). The capture reagent was an anti-ST2 mAb; captured ST2 was detected using an anti-ST2 polyclonal antibody. Concentrations below the LLOQ were fixed to LLOQ/2 (for functional itepekimab) or 0 (for total IL-33 and total sST2). Blood eosinophil counts were assessed using standard hematology assays in a central laboratory. Other biomarkers assessed included calcitonin (both studies), fractional exhaled nitric oxide (multiple-dose study only), and procalcitonin (single-dose study only).

Mean concentration–time profiles of functional itepekimab, total IL-33, total sST2, and percent change from baseline in blood eosinophils counts versus nominal time were plotted for both single- and multiple-dose studies on log-linear or linear scales. Noncompartmental analysis was performed to estimate the PK parameters for itepekimab after a single i.v. dose, a single s.c. dose, or multiple s.c. doses. The concentration–response relationships between functional itepekimab versus total IL-33 and median percent change from baseline in blood eosinophil levels in the multiple-dose study were assessed by hysteresis plots of the concentrations at each nominal time point.

A nonquantitative, titer-based bridging immunoassay was used to detect anti-itepekimab antibodies in serum, for which samples were collected prior to study drug administration, on day 85 (multiple-dose study only), and at the end of the study. The bridging ADA assay used a mouse anti-itepekimab mAb as the positive control and labeled drugs as the bridge components. Anti-itepekimab antibodies in samples bound with the labeled drugs, forming immune complexes. These complexes were captured on streptavidin-coated plates and detected by electrochemiluminescence. The ADA assay was validated as per the regulatory requirements with high sensitivity and drug tolerance (>400 μg/ml of itepekimab with 250 ng/ml of mouse positive control). Participants were classified as having a treatment-emergent ADA response to itepekimab if they had a negative ADA assay result or a missing result at baseline and subsequently had a positive ADA assay result post the first dose.

Safety was monitored via assessment of TEAEs, clinical laboratory tests, vital signs, and standard 12-lead ECGs at each visit.

Statistical analysis

No formal statistical hypotheses were tested, and no sample size calculations were performed. The safety analyses were performed descriptively on the safety populations, defined as all participants who received any study drug (active or placebo). Data for the placebo groups across doses were pooled within each study. PK, PD, and ADA responses were assessed for participants in the safety populations who had greater than or equal to one non-missing PK, PD, or ADA result, respectively, following the administration of the study drug. In addition to routine blinded safety analyses between cohorts for each study, interim analyses of unblinded data were conducted by designated teams for safety in the single-dose study greater than or equal to 16 weeks postdose for participants in all cohorts, and for safety and efficacy after the last patient completed day 15 in the multiple-dose study.

RESULTS

Patient characteristics

Forty participants (N = 30 itepekimab and N = 10 placebo) were enrolled in the single-dose study conducted from August 2016 to September 2017, and 23 (N = 17 itepekimab and N = 6 placebo) patients in the multiple-dose study conducted from January 2017 to September 2018. One participant in the placebo i.v. group of the single-dose study and two patients (1 each in the itepekimab 75 mg s.c. and 150 mg s.c. cohorts, respectively) in the multiple-dose study withdrew prior to completing the studies.

Baseline characteristics were similar across treatment groups within each study (Table 1). Patients in the multiple-dose study had similar baseline asthma characteristics (Table S1).

TABLE 1 Baseline characteristics

	Single-dose study									Multiple-dose study			
	I.V.					S.C.		Pooled data					
	Pooled placebo ($n = 8$)	0.3 mg/kg itepekimab ($n = 6$)	1 mg/kg itepekimab ($n = 6$)	3 mg/kg itepekimab ($n = 6$)	10 mg/kg itepekimab ($n = 6$)	Placebo ($n = 2$)	150 mg itepekimab ($n = 6$)	Placebo ($n = 10$)	Itepekimab ($n = 30$)	Pooled placebo ($n = 6$)	75 mg s.c. itepekimab ($n = 6$)	150 mg s.c. itepekimab ($n = 11$)	Pooled itepekimab ($n = 17$)
Age (years), mean (SD)	39.1 (15.7)	41.7 (15.2)	48.3 (14.8)	29.7 (9.1)	31.3 (14.2)	51.5 (7.8)	42.2 (9.9)	41.6 (15.0)	38.6 (14.0)	47.0 (10.4)	40.8 (7.1)	40.5 (11.6)	40.6 (10.0)
Sex (female), *n* (%)	5 (62.5)	5 (83.3)	4 (66.7)	4 (66.7)	4 (66.7)	1 (50.0)	5 (83.3)	6 (60.0)	22 (73.3)	3 (50.0)	3 (50.0)	5 (45.5)	8 (47.1)
BMI (kg/m^2), mean (SD)	24.9 (3.7)	22.2 (1.1)	27.3 (4.5)	23.3 (2.3)	24.3 (2.8)	25.9 (1.6)	26.0 (2.7)	25.1 (3.3)	24.6 (3.3)	26.1 (4.1)	25.1 (4.6)	27.6 (3.6)	26.7 (4.0)
Weight (kg), mean (SD)	72.9 (12.7)	62.7 (4.5)	81.7 (21.2)	66.9 (8.8)	72.2 (11.6)	73.5 (9.2)	74.2 (7.5)	73.0 (11.6)	71.5 (13.1)	77.8 (15.0)	70.1 (12.1)	81.4 (12.9)	77.4 (13.4)
Blood eosinophil count ($10^9/L$), mean (SD)	0.260 (0.131)	0.143 (0.085)	0.138 (0.104)	0.205 (0.150)	0.132 (0.087)	0.110 (0.071)	0.148 (0.135)	0.230 (0.134)	0.153 (0.110)	0.280 (0.158)	0.458 (0.598)	0.273 (0.113)	0.338 (0.358)

Note: Data collected at screening.

Abbreviation: BMI, body mass index.

TABLE 2 Mean (SD) noncompartmental pharmacokinetic parameters for itepekimab following i.v. or s.c. administration

	Single-dose study					Multiple-dose study	
PK parameter (units)	**0.3 mg/kg i.v. single dose ($n = 6$)**	**1 mg/kg i.v. single dose ($n = 6$)**	**3 mg/kg i.v. single dose ($n = 6$)**	**10 mg/kg i.v. single dose ($n = 6$)**	**150 mg s.c. single dose ($n = 6$)**	**75 mg s.c. q.w. ×4 ($n = 6$)**	**150 mg s.c. q.w. ×4 ($n = 10$)**
C_{max} (mg/L)	8.9 (2.1)	39.1 (4.0)	104 (13.5)	360 (28.5)	18.6 (3.0)	29.1 (7.1)	45.3 (10.6)
T_{max} (day)[a]	0.0833 (0.0833–0.208)	0.0629 (0.0424–0.0833)	0.0826 (0.0431–0.205)	0.146 (0.0424–0.209)	9.17 (2.97–16.2)	27.5 (20.0–30.0)	28.0 (28.0–28.0)
AUC_{inf} (mg·d/L)	184 (41)	598 (89)	2070 (260)	7410 (1220)	926 (280)	1770 (520)	2820 (920)
AUC_{extrap} (%)	9.42 (2.80–12.6)	2.64 (0.653–10.7)	1.29 (0.296–2.45)	0.240 (0.0877–13.2)	1.77 (0.542–4.33)	0.733 (0.603–6.38)	0.413 (0.161–4.95)
$t_{1/2}$ (day)	31.6 (7.2)	30.3 (4.5)	31.1 (4.4)	30.0 (3.5)	30.9 (4.8)	30.0 (3.0)	31.0 (5.1)
CL or CL/F (ml/day/kg)[b,c]	1.71 (0.41)	1.71 (0.27)	1.47 (0.19)	1.38 (0.19)	2.34 (0.55)	2.61 (0.66)	2.77 (0.63)
V_{ss} (ml/kg)	69.8 (14.5)	64.5 (3.6)	57.5 (7.3)	54.2 (3.6)	–	–	–
C_{max}/dose (mg/L/mg)[d]	0.476 (0.130)	0.499 (0.104)	0.527 (0.096)	0.507 (0.068)	0.124 (0.020)	0.388 (0.094)	0.302 (0.070)
AUC_{inf}/dose (mg·day/L/mg)[c]	9.83 (2.42)	7.70 (2.09)	10.5 (2.36)	10.4 (1.71)	6.17 (1.87)	5.90 (1.73)	4.71 (1.54)

Abbreviations: AUC, area under the curve; AUC_{extrap},extrapolated portion of AUC_{inf}; AUC_{inf}, AUC from the time of dosing to the last measurable concentration and extrapolated to infinity; CL, clearance; C_{max}, maximum serum concentration; C_{trough}, trough concentration; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; T_{max}, time to maximum concentration; V_{ss}, steady state volume of distribution.

[a]T_{max} and AUC_{extrap} presented as median (minimum–maximum).

[b]Reported as CL for i.v. doses and CL/F for s.c. doses.

[c]In the multiple-dose study, total dose (75 mg ×4 or 150 mg ×4) was used to calculate CL/F (dose/AUC_{inf}/body weight) and AUC_{inf}/dose.

[d]In the multiple-dose study, weekly dose (75 mg or 150 mg) was used to calculate C_{max}/dose.

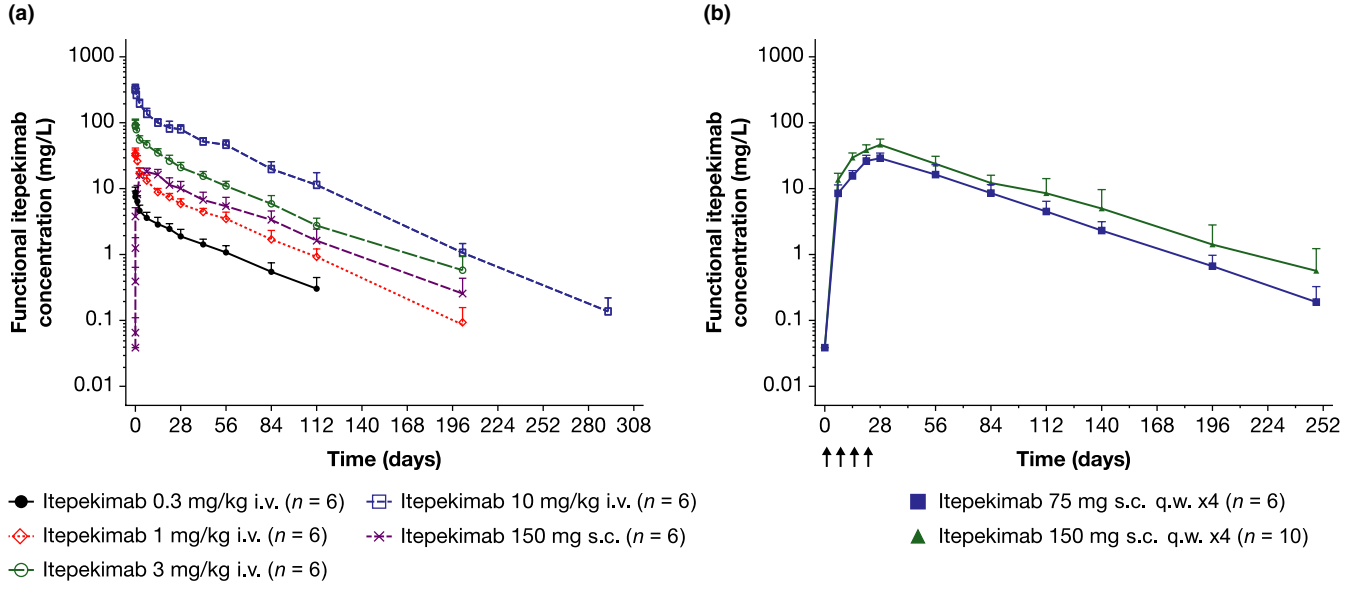

FIGURE 1 Mean (+SD) log-scaled concentration of functional itepekimab in serum versus nominal time in the (a) single-dose and (b) multiple-dose studies. Arrows indicate itepekimab s.c. administration at days 1, 8, 15, and 22 in the multiple-dose study

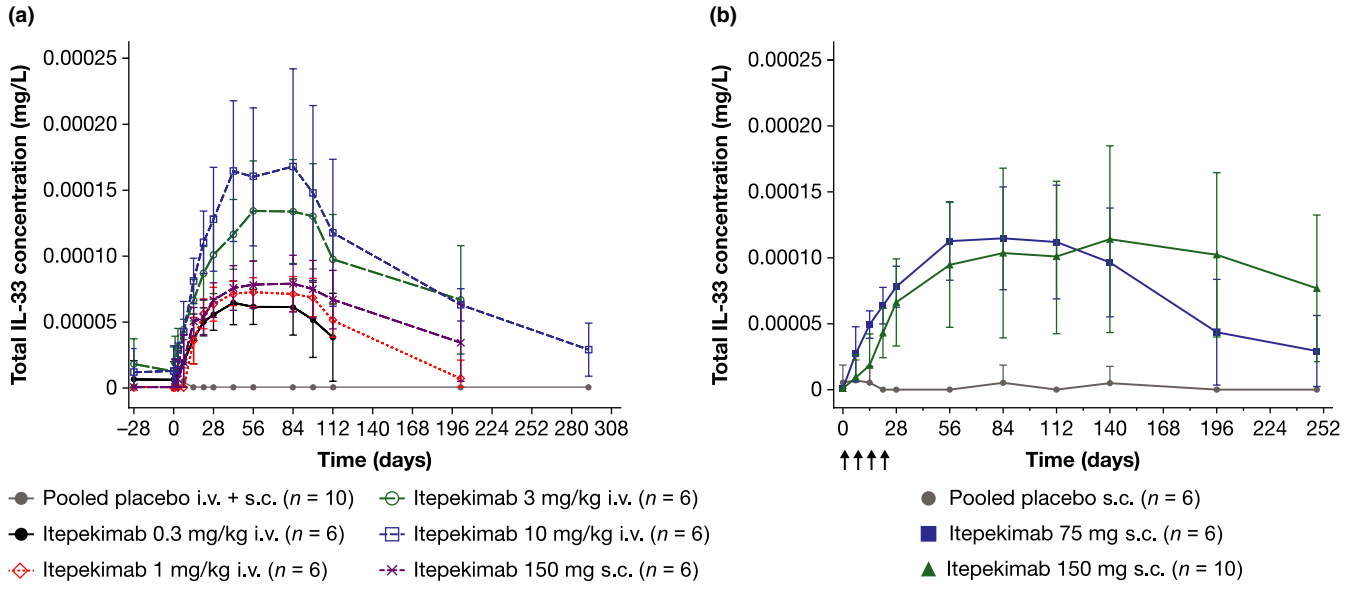

FIGURE 2 Mean (±SD) concentration of total IL-33 in serum versus nominal time in the (a) single-dose and (b) multiple-dose studies. Arrows indicate itepekimab s.c. administration at days 1, 8, 15, and 22 in the multiple-dose study. Error bars extending below 0 mg/L were removed

Itepekimab pharmacokinetics

A summary of PK parameters calculated from concentrations of functional itepekimab in serum is presented by treatment group in Table 2 for both studies. Across the studied dose ranges in both single- and multiple-dose trials, mean (Figure 1) and individual (Figure S1) profiles demonstrated linear PKs.

In the single-dose study, maximum concentrations of functional itepekimab in serum were achieved immediately following i.v. administration and ~ 9 days following s.c. administration (Figure 1a). Within the i.v. cohorts, itepekimab exposure increased in a dose-proportional manner, as confirmed by mean maximum concentration (C_{max})/dose and area under the curve to infinity (AUC_{inf})/dose following i.v. doses of 0.3–10 mg/kg (Table 2). Mean clearance (CL) and steady-state volume (V_{ss}) estimates decreased slightly over the i.v. dose range studied, although the between-participant variability in these estimates did not support a meaningful trend (Table 2). Mean $t_{1/2}$ following a single i.v. or s.c. dose was 30.0–31.6 days and appeared to be independent of dose and concentration

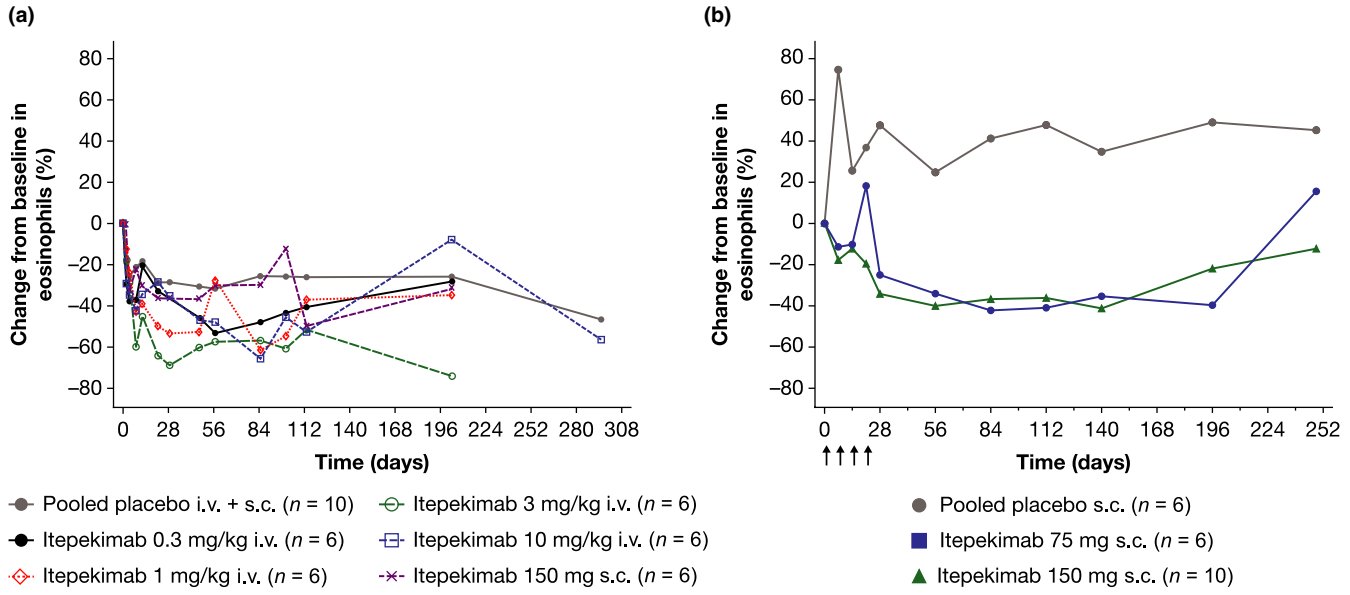

FIGURE 3 Median percent change from baseline in blood eosinophils versus nominal time in the (a) single-dose and (b) multiple-dose studies. Arrows indicate itepekimab s.c. administration at days 1, 8, 15, and 22 in the multiple-dose study

TABLE 3 TEAEs in the single-dose study safety population

	Single-dose study	
***n* (%)**	**Pooled i.v. + s.c. placebo (*n* = 10)**	**Pooled i.v. + s.c. itepekimab (*n* = 30)**
Patients with any TEAE	9 (90.0)	26 (86.7)
Patients with any serious TEAE	0	0
Patients with any severe TEAE	0	1 (3.3)
TEAEs reported by ≥2 patients in any treatment cohort by preferred term		
Influenza-like illness	1 (10.0)	5 (16.7)
Fatigue	1 (10.0)	4 (13.3)
Chest pain	0	2 (6.7)
Viral upper respiratory tract infection	1 (10.0)	10 (33.3)
Headache	4 (40.0)	9 (30.0)
Dizziness	2 (20.0)	3 (10.0)
Oropharyngeal pain	1 (10.0)	9 (30.0)
Dyspnea exertional	2 (20.0)	2 (6.7)
Back pain	1 (10.0)	3 (10.0)
Pain in extremity	2 (20.0)	1 (3.3)
Palpitations	1 (10.0)	4 (13.3)
Rash papular	2 (20.0)	1 (3.3)

Note: Participants who reported ≥2 TEAEs with the same preferred term were counted only once for that term. Participants who reported ≥2 TEAEs with different preferred terms within the same system organ class were counted only once in that system organ class.

Abbreviation: TEAE, treatment-emergent adverse event.

(Table 2). Based on the ratio of mean CL for each i.v. cohort relative to apparent CL of the s.c. cohort (CL/F), absolute bioavailability of itepekimab was estimated to be 59%–73%.

In the multiple-dose study, functional itepekimab concentrations in serum increased over the first 4 weeks of weekly 75 mg or 150 mg s.c. injections and demonstrated accumulation following multiple doses (Figure 1b).

Maximum concentrations of functional itepekimab were observed around 28 days after the start of treatment and 7 days after the final s.c. dose (Table 2). Consistent with the single-dose study, the mean $t_{1/2}$ of functional itepekimab in patients with moderate asthma was 30.0–31.0 days and independent of dose (Table 2). C_{max}/dose and AUC_{inf}/dose were ~ 20% lower for the itepekimab 150 mg dose group than for the 75 mg dose group, but body weight-adjusted CL/F was similar in both groups (Table 2).

Itepekimab pharmacodynamics

Total IL-33 concentrations increased following administration of itepekimab in both the single- and multiple-dose studies. IL-33 was below the LLOQ at baseline in most healthy participants and patients with asthma, with measurable concentrations typically appearing within 14 days after administration of itepekimab. IL-33 remained below or near the LLOQ for placebo groups throughout the single-dose (Figure 2a) and multiple-dose (Figure 2b) studies.

In the single-dose study, IL-33 concentrations in serum responded to itepekimab in a dose-dependent fashion, with IL-33 increases observed at earlier time points with higher itepekimab doses. Higher plateau IL-33 concentrations were observed with higher doses of itepekimab (3 mg/kg i.v. and 10 mg/kg i.v.) compared with the 0.3 mg/kg and 1 mg/kg i.v. doses and the 150 mg s.c. dose (Figure 2a). In the multiple-dose study, both s.c. doses achieved similar plateaus in IL-33 concentration; however, the increases were more durable for the 150 mg s.c. dose (Figure 2b). Individual IL-33 profiles for the single and multiple-dose studies are shown in Figure S2a,b, respectively.

Blood eosinophil counts decreased rapidly in the single-dose study, and this was maintained throughout the study period, but interpretation was complicated by decreasing trends in both placebo- and itepekimab-treated patients (Figure 3a). In the multiple-dose study, both doses of itepekimab reduced eosinophil counts by ~ 35%–40%. A median decrease was observed at the end of study visit for the 150 mg dose, whereas eosinophil levels were above baseline for the 75 mg dose (Figure 3b). Following multiple s.c. doses, temporal delays were noted between changes in itepekimab concentrations and total IL-33 concentrations (Figure S3a) or percent change in blood eosinophil counts (Figure S3b). During the off-treatment follow-up period, the PD effects (IL-33 increase and eosinophil reduction) diminished once median itepekimab concentrations fell below ~ 5–10 mg/L for both dose levels.

Mean concentrations of total sST2 in serum were not affected by itepekimab administration and remained constant over the course of both studies (Figure S4). No changes in the levels of other biomarkers were observed.

Safety

Single doses of itepekimab up to 10 mg/kg i.v. and 150 mg s.c. were well-tolerated by healthy adults. There were no dose-limiting toxicities and a maximum tolerated dose was not reached. There were no deaths or serious TEAEs. One female patient in the itepekimab 0.3 mg/kg i.v. group had two severe TEAEs—two episodes of transient chest pain—which were considered by the investigator to be related to itepekimab. These episodes occurred on day 24 and day 27, lasted ~ 10 min each, and resolved spontaneously with normal ECG, creatine kinase levels, and normal clinical evaluation. The rates of TEAEs were similar in itepekimab- versus placebo-treated patients (26/30 [86.7%] vs. 9/10 [90.0%]; Table 3). Influenza-like illness, viral upper respiratory

TABLE 4 TEAEs in the multiple-dose study safety population

	Multiple-dose study	
***n* (%)**	**Placebo pooled (*n* = 6)**	**Itepekimab pooled (*n* = 17)**
Patients with any TEAE	5 (83.3)	13 (76.5)
Patients with any serious TEAE	0	0
Patients with any severe TEAE	0	0
TEAEs reported by ≥20% patients in any treatment cohort by preferred term		
Headache	1 (16.7)	4 (23.5)
Gastroenteritis	2 (33.3)	1 (5.9)
Nasopharyngitis	2 (33.3)	1 (5.9)

Note: Patients who reported ≥2 TEAEs with the same preferred term were counted only once for that term. Patients who reported ≥2 TEAEs with different preferred terms within the same system organ class were counted only once in that system organ class.

Abbreviation: TEAE, treatment-emergent adverse event.

tract infection, oropharyngeal pain, palpitations, and chest pain were reported in higher percentages of participants in the pooled (i.v. and s.c.) itepekimab group than in the pooled (i.v. and s.c.) placebo group (Table 3). There were no clinically meaningful changes in laboratory values, vital signs, or ECGs.

In the multiple-dose study in patients with moderate asthma, itepekimab was overall well-tolerated. The proportions of patients reporting greater than or equal to one TEAE were similar in the pooled itepekimab and pooled placebo groups (13/17 [76.5%] vs. 5/6 [83.3%]). No serious or severe TEAEs, deaths, or TEAEs leading to withdrawal were reported (Table 4). The most common TEAEs were headache (placebo 16.7% vs. itepekimab 23.5%), gastroenteritis (33.3% vs. 5.9%), and nasopharyngitis (33.3% vs. 5.9%; Table 4).

No clinically significant changes in laboratory values, vital signs, ECGs, or physical examinations were attributed to itepekimab. The proportion of patients with predefined treatment-emergent potentially clinically significant values for laboratory, ECG, and vital signs parameters were generally similar between s.c. itepekimab- and placebo-treated groups except for hematology values, which were lower in the pooled s.c. itepekimab group (29.4%) than in the pooled placebo group (83.3%).

Anti-drug antibodies

None of the participants in either study had a treatment-emergent ADA response following itepekimab administration. All participants were also ADA-negative at baseline.

DISCUSSION

The two studies described here present the initial safety experience of itepekimab in healthy adults and patients with moderate asthma. The PKs of single and multiple doses were also characterized as well as the PDs of itepekimab.

Itepekimab exhibited linear and dose-proportional PKs following a single dose in healthy participants across the dose ranges studied and following multiple doses in patients with moderate asthma. Itepekimab was well-absorbed following s.c. injection and demonstrated a long $t_{1/2}$, supporting less frequent dosing regimens in subsequent studies. Indeed, following observations in the initial single dose 0.3 mg/kg cohort, a longer follow-up period was incorporated for the remaining cohorts in the single-dose study and in the multiple-dose study to ensure adequate characterization of study end points. No treatment-emergent ADA responses were observed, and itepekimab was generally well-tolerated across studies.

Total IL-33 concentrations in serum of healthy participants and patients with asthma were mostly undetectable at baseline, which is consistent with low systemic IL-33 concentrations reported in a population of patients with COPD.[28] Serum IL-33 concentrations increased in response to itepekimab administration. This effect is consistent with the biology of alarmins[21]; IL-33 is a short-lived molecule stabilized by binding to itepekimab. Given the low-to-undetectable concentrations of IL-33 at baseline, the total IL-33 detected following treatment with itepekimab is likely to exist predominantly as a complex between IL-33 and itepekimab, serving as a marker of target engagement. The rate of decline of total IL-33 concentrations in both studies was considerably slower than may be expected from the $t_{1/2}$ of itepekimab alone and may indicate that the elimination of the itepekimab–IL-33 complex occurs more slowly than that of itepekimab alone. Dose-dependent increases in total IL-33 levels were observed in the single-dose study, with notable overlap of profiles for individuals receiving single 3 mg/kg or 10 mg/kg i.v. doses, suggesting saturation of binding at these higher doses. A similar early time course of total IL-33 was also observed for the 75 mg and 150 mg doses in the multiple-dose study, but elevations were more durable in the 150 mg group than in the 75 mg group. It is unclear why differentiation at later time points was inconsistent between dose levels that achieved initial saturation in both studies, but less frequent sampling density in the single-dose study may have played a role. Exploration of the relationship between itepekimab dose and target concentrations will continue in future studies.

Blood eosinophil counts decreased over the first 4 weeks of treatment in response to itepekimab administration across doses in both studies. No changes to other systemic biomarkers were observed, including sST2, but this does not exclude tissue-specific changes not reflected in serum levels. The lack of change in sST2 levels is supported by the preclinical HDM extract mouse model, in which ST2 gene (*Il1rl1*) expression was upregulated in response to HDM treatment; however, IL-33 blockade by itepekimab restored ST2 to normal levels.[26]

The extent of reduced eosinophil counts reported here with itepekimab-mediated inhibition of the IL-33 pathway is less than that observed for the anti–IL-5 antibody mepolizumab, which reduced eosinophil counts by up to 86% in patients with severe eosinophilic asthma.[10,11,29] IL-33 acts as an alarmin upstream of IL-5, and its role in maintaining IL-5 levels may promote eosinophil survival.[30] Eosinophil reductions observed in these studies could result from the secondary regulation of IL-5, but IL-33 is expected to have a broader impact on type 1 and 2 inflammation than

simply inhibiting IL-5 alone. Reduction of eosinophil levels might be just one facet of the anti-inflammatory effect of IL-33 blockade, which will be explored in future clinical trials assessing the efficacy of itepekimab in inflammatory airway diseases.

Loss of eosinophil suppression and sharp decreases in IL-33 concentrations were observed at itepekimab concentrations below 5 mg/L for both doses evaluated in the multiple-dose study. However, the presence of hysteresis loops in these relationships indicated temporal delays characteristic of indirect responses and consistent with the reported roles of IL-33 in promoting eosinophil development and survival.[31] Where concentration–response of indirect relationships, such as these are informed predominantly by declining concentrations, observed threshold concentrations may represent an underestimation of those needed to maintain an associated PD effect. These clinical studies were interpreted in concert with preclinical dose-ranging studies in the HDM mouse model to identify a consensus target concentration range associated with an optimal impact on systemic PD markers in humans and lung inflammation end points in mice. Modeling and simulation approaches incorporating the data reported here were used to select the itepekimab 300 mg s.c. every 2 weeks regimen for subsequent phase II studies to evaluate inhibition of the IL-33 pathway in chronic airway inflammation, either as a monotherapy or in combination with other targeted therapies.

The limitations of these studies include the small sample sizes and that the PDs of itepekimab were evaluated in a population in which the majority did not have asthma. Furthermore, the treatment period assessed in the multiple-dose study was only 4 weeks. Based on the dosing regimens of other anti-inflammatory biologics approved to treat asthma, long-term administration of itepekimab will likely be required to treat chronic airway diseases. Despite these limitations, the PD effects of itepekimab observed in these studies are consistent with the larger phase II clinical trial that demonstrated the clinical efficacy of itepekimab in asthma.[32]

In conclusion, these studies have shown that itepekimab is well-tolerated in healthy participants and patients with moderate asthma, is well-absorbed following s.c. injection, and demonstrates linear and dose-proportional PKs without evidence of ADA responses. Elevated total IL-33 concentrations demonstrated target engagement, with blood eosinophil count reduction appearing to demonstrate PD activity.

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CONFLICT OF INTEREST

M.P.K., G.D.K., S.H., C.L., W.Z., J.D.D., and M.A.K. are employees and shareholders of Regeneron Pharmaceuticals, Inc. C.R.X. is an employee of Sanofi and may hold stock and/or stock options in the company.

AUTHOR CONTRIBUTIONS

M.P.K., G.D.K., C.R.X., S.H., C.L., W.Z., J.D.D., and M.A.K. wrote the manuscript. G.D.K., C.R.X., S.H., J.D.D., and M.A.K. designed the research. W.Z. performed the research. M.P.K., G.D.K., C.R.X., S.H., C.L., W.Z., J.D.D., and M.A.K. analyzed the data.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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