Article:

ARTICLE

Pharmacokinetics and pharmacodynamics of itepekimab in adults with moderate-to-severe atopic dermatitis: Results from two terminated phase II trials

Matthew P. Kosloski[1] | Emma Guttman-Yassky[2,3] | Michael J. Cork[4,5] |
Margitta Worm[6] | Dong-Ho Nahm[7] | Xiaoping Zhu[8] | Marcella K. Ruddy[1] |
Sivan Harel[1] | Mohamed A. Kamal[1] | Hélène Goulaouic[9] | Christine R. Xu[10] |
Elena Avetisova[1] | John D. Davis[1] | Michael C. Nivens[11] | Arsalan Shabbir[11] |
Allen Radin[1]

[1]Regeneron Pharmaceuticals Inc.,
Tarrytown, New York, USA

[2]Icahn School of Medicine at Mount
Sinai Medical Center, New York, New
York, USA

[3]Rockefeller University, New York, New
York, USA

[4]Sheffield Dermatology Research,
University of Sheffield, Sheffield, UK

[5]Sheffield Children's Hospital, Sheffield,
UK

[6]Division of Allergy and Immunology,
Department of Dermatology,
Venerology and Allergy, Charité-
Universitätsmedizin Berlin, Berlin,
Germany

[7]Ajou University Hospital, Suwon, Korea

[8]Formerly Regeneron Pharmaceuticals
Inc., Basking Ridge, New Jersy, USA

[9]Sanofi, Chilly-Mazarin, France

[10]Sanofi, Bridgewater, New Jersey, USA

[11]Formerly Regeneron Pharmaceuticals,
Tarrytown, New York, USA

Correspondence
Matthew P. Kosloski, Regeneron
Pharmaceuticals Inc., 777 Old Saw Mill
River Road, Tarrytown, NY 10591, USA.
Email: matthew.kosloski@regeneron.
com

Abstract

Interleukin-33 (IL-33) is a proinflammatory alarmin cytokine released by dam-aged epithelial tissue cells that initiates and amplifies both type 1 and type 2 inflammatory cascades. A role for IL-33 in atopic dermatitis (AD; a chronic, re-lapsing type 2 inflammatory disease of the skin) has been proposed. Itepekimab is a novel human IgG4P monoclonal antibody against IL-33, currently in clini-cal development for chronic obstructive pulmonary disease (COPD). Two global phase II studies—a dose-ranging itepekimab monotherapy study (NCT03738423) and a proof-of-concept study of itepekimab alone and in combination with dupilumab (NCT03736967)—were conducted in patients with moderate-to-severe AD to assess safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy; both studies were terminated following an interim analysis of the proof-of-concept study, which failed to demonstrate the efficacy of itepekimab. In these two studies, itepekimab exhibited linear and dose-proportional pharma-cokinetics. Pharmacodynamics of total IL-33 indicated that itepekimab saturated binding to the target in serum at 300 mg q2w and q4w doses, and decreased blood eosinophil counts. Concentration–time profiles of itepekimab and total IL-33 were similar for itepekimab with or without dupilumab, and between East Asian and non-East Asian subgroups. Itepekimab was generally well tolerated, both alone and in combination with dupilumab. The lack of clinical efficacy for itepe-kimab observed in these studies suggests that IL-33 may not be a key pathogenic driver in moderate-to-severe AD.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Interleukin-33 (IL-33), a proinflammatory alarmin cytokine released by damaged epithelial tissue cells, initiates and amplifies both type 1 and type 2 inflammatory cascades. IL-33 has been suggested as having a role in atopic dermatitis (AD), a chronic, relapsing type 2 inflammatory disease of the skin. Itepekimab is a novel human IgG4P monoclonal antibody against IL-33, currently in development for chronic obstructive pulmonary disease (COPD).

WHAT QUESTION DID THIS STUDY ADDRESS?

Is itepekimab safe and well tolerated in patients with moderate-to-severe AD? What are the pharmacokinetic and pharmacodynamic profiles of itepekimab during treatment in this population? Is itepekimab treatment efficacious in this population, either alone or in combination with dupilumab?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Itepekimab was generally well tolerated, both alone and in combination with dupilumab, and no anti-drug antibodies to itepekimab were observed in either study. Both itepekimab monotherapy and the combination of itepekimab and dupilumab were well tolerated in adults with moderate-to-severe AD. In these studies, itepekimab demonstrated linear and dose-proportional pharmacokinetics, which were similar in East Asian and non-East Asian subgroups; pharmacokinetics for itepekimab were similar with and without dupilumab. Pharmacodynamics of total IL-33 in serum indicated that itepekimab engaged the target and saturated binding in serum at 300 mg q2w and q4w doses; similar increases in IL-33 were observed with and without dupilumab. Itepekimab lacked efficacy in both studies, which were terminated following an interim analysis of the proof-of-concept study.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The lack of clinical efficacy observed in these studies suggests that IL-33 may not be a primary pathogenic driver in chronic moderate-to-severe AD. However, the pharmacokinetic and pharmacodynamic profiles of itepekimab characterized in this study are applicable to other Type 2 indications in which efficacy was demonstrated.

INTRODUCTION

Interleukin-33 (IL-33), a proinflammatory alarmin cytokine that initiates and amplifies innate and adaptive inflammatory cascades, is released by damaged epithelial tissue cells in response to insults, such as allergens, viruses, or other environmental triggers.[1] When IL-33 binds to its cognate receptor (ST2) and engages the interleukin-1 receptor accessory protein, signaling activates multiple downstream inflammatory pathways, resulting in the initiation and amplification of type 1 and type 2 inflammatory cascades.[2]

Evidence suggests a role for IL-33 in atopic dermatitis (AD), a chronic, relapsing type 2 inflammatory disease of the skin that is characterized by pruritus, xerosis, and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification.[3–6] IL-33 is typically not detectable in healthy tissue or blood but is overexpressed in keratinocytes of patients with AD, disrupting skin barrier function and promoting itch.[7] IL-33 can stimulate group 2 innate lymphoid cells (ILC2), which are enriched in lesions of AD skin, to produce type 2 cytokines that further contribute to barrier dysfunction and eosinophilic inflammation.[7]

Itepekimab, also known as REGN3500 or SAR440340, is a novel human VelocImmune®-derived[8,9] IgG4P monoclonal antibody (mAb) against IL-33. In phase I studies, itepekimab demonstrated dose-proportional linear pharmacokinetics (PK) with a long terminal half-life of 30.0–31.6 days in healthy subjects and patients with asthma following intravenous or subcutaneous doses.[10] In both populations, itepekimab administration

led to increases in total serum IL-33 concentrations and decreased blood eosinophils, with durable effect.[10] In a phase II trial in patients with asthma, itepekimab monotherapy reduced the frequency of loss of asthma control events and improved lung function; however, the combination of itepekimab and dupilumab resulted in no additional observed beneficial effects over itepekimab monotherapy.[11] In a phase II trial in chronic obstructive pulmonary disease (COPD), itepekimab versus placebo did not meet the primary endpoint in the overall population; however, itepekimab reduced acute COPD exacerbations and improved lung function in the prespecified former-smoker subgroup.[12] Two phase III studies of itepekimab in COPD are currently ongoing (NCT04701983, NCT04751487).

Dupilumab, a fully human mAb[8,13] that blocks the shared receptor component for IL-4/IL-13 and decreases markers of type 2 inflammation, is approved for the treatment of AD, with or without concomitant topical steroid use.[14–18] However, some patients do not achieve complete responses as defined by Investigator's Global Assessment (IGA) 0/1 (clear or nearly clear skin).[19–21] A mouse model of airway inflammation suggests that simultaneous inhibition of the IL-4/IL-13 and the IL-33 cytokine pathways may have additive effects.[22] It was hypothesized that broad inhibition of type 2 and non-type 2 inflammation with a combination of itepekimab and dupilumab could further improve the efficacy of dupilumab in AD, potentially yielding a sustained duration of action and incrementally additive efficacy.

Despite successful clinical trials with treatments targeting alarmins such as IL-33 and thymic stromal lymphopoietin (TSLP) in airway diseases including asthma and COPD,[11,12,23] translation to clinical outcomes in AD for anti-alarmins have not met expectations. In a phase IIa study, treatment with the anti-TSLP mAb tezepelumab did not demonstrate statistically significant improvements in the primary end point, the proportion of patients achieving 50% reduction in Eczema Area and Severity Index (EASI) score.[24] Similarly, despite significant improvements in EASI scores for patients with AD following a single intravenous dose of the anti-IL-33 mAb etokimab in a small, open-label phase IIa study, in the larger phase IIb placebo-controlled study, it failed to improve EASI scores relative to placebo.[25,26] However, it was unclear to what extent outcomes in that phase IIb study were specific to etokimab and the design of that study or generalizable to the anti-IL-33 mechanism of action.

In this analysis, two phase II studies, a multiple subcutaneous dose-ranging itepekimab monotherapy study (NCT03738423) and a proof-of-concept study of multiple subcutaneous itepekimab doses alone and in combination with dupilumab (NCT03736967), were conducted

in patients with moderate-to-severe AD; the studies were conducted simultaneously and terminated following an interim analysis of the proof-of-concept study showing lack of itepekimab efficacy. In the proof-of-concept study, no significant difference was found compared with placebo, and no incremental benefit was seen from itepekimab plus dupilumab dual therapy. Once discontinued, patients in both studies entered the follow-up period, and blinding was maintained through last-patient last-visit.

Here, we report on the PK and pharmacodynamic (PD) properties of itepekimab, as well as the observed safety profile, in patients with moderate-to-severe AD enrolled in these two trials.

METHODS

Study designs and patients

Studies were conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonization Guideline for Good Clinical Practice and applicable regulatory requirements. Informed consent was obtained from each patient prior to study enrollment. 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 studies.

The dose-ranging phase IIb trial was a randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy, safety, and pharmacokinetic profiles of itepekimab in adults with moderate-to-severe AD (Figure 1a). Patients were randomized to subcutaneous (SC) itepekimab 300 mg every 2 weeks (q2w), 300 mg every 4 weeks (q4w), 100 mg q4w, 30 mg every 8 weeks (q8w), or placebo q2w for 16 weeks, with a 20-week follow-up period. Itepekimab was administered as one 2 mL and one 1 mL injections (300 mg), one 1 mL injection (100 mg), or one 0.3 mL injection (30 mg). Additional placebo injections were administered to patients on active drugs during the treatment period to maintain blinding between regimens. Patients were enrolled from seven countries: Australia, Canada, Czechia, Germany, Hungary, Japan, Poland, Republic of Korea, Spain, and the United States.

The proof-of-concept phase IIa trial was a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of itepekimab as monotherapy and in combination with dupilumab in adults with moderate-to-severe AD (Figure 1b). Participants were randomized to SC itepekimab 300 mg q2w, dupilumab 300 mg q2w, itepekimab 300 mg q2w + dupilumab 300 mg q2w, or placebo q2w for 16 weeks,
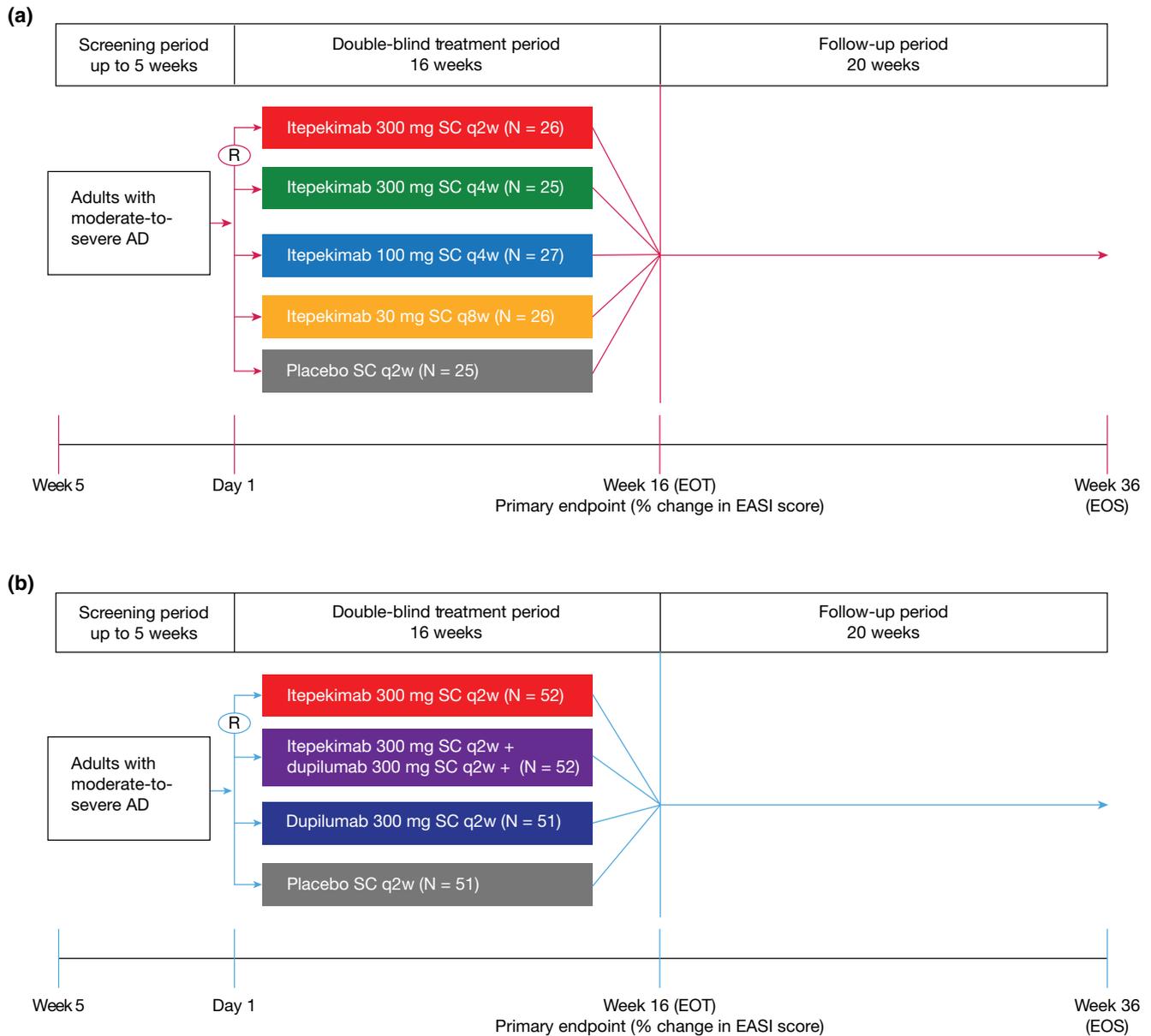
FIGURE 1 Study designs of the (a) dose-ranging study and (b) proof-of-concept study. Dupilumab arms included a 600 mg loading dose on day 1. Following an interim analysis of the proof-of-concept study indicating a lack of efficacy, both studies were terminated; once discontinued, patients in the treatment period entered the 20-week follow-up period at their next study visit. AD, atopic dermatitis; D, day; EASI, Eczema Area and Severity Index; EOS, end of study; EOT, end of treatment; N, enrolled population; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; R, randomization; SC, subcutaneous; W, week.

with a 20-week follow-up period. Itepekimab was administered as one 2 mL and one 1 mL injections (300 mg) and dupilumab was administered as one 2 mL injection (300 mg) or two 2 mL injections (600 mg loading dose). Additional placebo injections were administered to patients on active drugs during the treatment period to maintain blinding between regimens. Dupilumab regimens were administered with a 600 mg loading dose upon initial injection. Patients were enrolled from seven countries: Belgium, Czechia, Germany, Poland, Republic of Korea, Spain, and United States.

Eligible patients in both studies were aged 18–75 years, with chronic AD present for at least 3 years prior to

screening. Other inclusion criteria included EASI score ≥16, IGA score ≥3, ≥10% body surface area (BSA) of AD involvement, weekly average of daily Peak Pruritus Numerical Rating Scale (PP-NRS) score ≥4, and documented history of inadequate response to topical AD medication. Exclusion criteria included participation in a prior anti-IL-33 class medication clinical study; body mass index <16 kg/m^2; active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline; and the presence of skin comorbidities that may interfere with study assessments.

An interim data analysis was conducted for the proof-of-concept study by an unblinded management team. This analysis indicated that the efficacy of itepekimab monotherapy in patients with moderate-to-severe AD was not compelling when compared with the dupilumab-positive control arm. Additionally, no incremental benefit or increased duration of action was seen in the itepekimab plus dupilumab combination therapy arm compared with dupilumab monotherapy. As a result of this lack of efficacy, a decision was made to terminate both ongoing studies. Patients in the treatment period were discontinued from the study drug and entered the 20-week follow-up period at their next study visit. The study team that was involved in the conduct of the study remained blinded until the database lock.

Outcomes

The primary efficacy end point for both studies was the percent change from baseline in EASI score at Week 16. Secondary end points included concentration–time profiles of functional itepekimab in serum and incidence of treatment-emergent anti-drug antibodies (ADAs) responses to itepekimab. Concentrations of total IL-33 in serum and percent change from baseline in blood eosinophil counts over time were also assessed.

Study assessments

In both studies, samples for measurement of drug concentrations and total IL-33 were collected at baseline and weeks 2, 4, 8, 12, and 16 during the treatment period, and weeks 20, 24, 28, 32, and 36 during the follow-up period. Samples for determination of ADAs were collected at baseline, Week 16, and Week 36. Additional intensive PK sampling was performed 1, 3, and 7 days after the first dose. Six patients from Japan were enrolled in the dose-ranging study. All samples were collected prior to administration of the study drug on dosing days.

Using methods previously reported,[10] concentrations of functional itepekimab (i.e., itepekimab with ≥1 unoccupied binding site) in serum were measured using a validated enzyme-linked immunosorbent assay (ELISA) on serum samples taken before each dose (lower limit of quantification [LLOQ] = 0.078 mg/L) and at the end of the study. The functional itepekimab PK assay utilized itepekimab as the assay standard and human IL-33 as the capture reagent. Concentrations of functional itepekimab below the LLOQ were fixed to LLOQ/2.

Concentrations of total IL-33, which includes free IL-33 and IL-33 bound to itepekimab or soluble ST2 (sST2),

were determined from serum samples using an electrochemiluminescence immunoassay (LLOQ = 31.3 pg/mL). The assay included acid pretreatment of serum samples to improve the 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. Concentrations of total IL-33 below the LLOQ were fixed to zero.

ADAs in serum were assessed using a validated electrochemiluminescence bridging immunoassay that employs a mouse anti-itepekimab mAb as the positive control and labeled drugs as the bridge components. The assay involves potentially three different evaluations: an initial screen, a confirmation assay based on competition, and a measurement of the titer of anti-itepekimab antibodies in a sample. Patients 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 after the first dose.

Safety was monitored via assessment of treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, and standard 12-lead electrocardiograms (ECG).

Statistical analysis

Due to the premature termination of the study, no formal statistical analyses were performed, and all summaries presented are descriptive statistics. Functional itepekimab concentrations were analyzed in all randomized patients who received any dose of itepekimab and who had at least one non-missing concentration result following the first dose of the study drug. Total IL-33 concentrations were analyzed in all randomized patients who received any dose of the study drug (active or placebo) and who had at least one non-missing concentration result following the first dose of study drug. ADAs to itepekimab were analyzed in all patients who received any study drug (active or placebo) and who had at least one non-missing ADA result after the first dose of study drug. Safety end points, including blood eosinophil counts, were analyzed in all randomized patients who received any study drug (active or placebo). EASI scores were analyzed in all randomized patients. For efficacy assessments, data after rescue treatment was set to missing.

Analyses of function itepekimab, total IL-33, and blood eosinophils over time included all data for patients who completed the study per the original protocol, and data from patients who prematurely discontinued treatment was included for the remainder of the dosing interval after the last dose for pharmacokinetic and pharmacodynamic assessments (e.g., 2, 4, or 8 weeks after the last

dose for patients receiving q2w, q4w, or q8w regimens, respectively). All collected samples were included for determination of ADA status, irrespective of study drug discontinuation. Safety assessments utilized all collected data.

RESULTS

Patient characteristics

In both studies, baseline demographics and disease characteristics were generally similar across treatment groups (Table 1). In the proof-of-concept study, there was a lower proportion of East Asian and non-East Asian patients in the dupilumab group (19.6%, 10/51) and a higher proportion in the placebo group (46.0%, 23/50), compared with 30.8% (16/52) in the itepekimab group and 36.5% (19/52) in the itepekimab plus dupilumab groups.

Itepekimab exposure

Due to the early termination of these two studies, only 34.1% (44/129) of randomized patients in the dose-ranging study and 29.1% (60/206) of randomized patients in the proof-of-concept study completed the 16-week treatment period. The duration of treatment exposure by dose group for patients who received the study drug in each study is provided in Tables S1 and S2.

Itepekimab pharmacokinetics

Concentration–time profiles of itepekimab in the dose-ranging study and proof-of-concept study are shown in Figure 2a,b, respectively. In the dose-ranging study, mean concentration–time profiles exhibited parallel terminal elimination slopes (linear PK) (Figure 2a). Concentration–time profiles for itepekimab 300 mg q2w were similar to those for monotherapy or with dupilumab in the proof-of-concept study, and coadministration of dupilumab did not affect the itepekimab PK profile (Figure 2b).

In the dose-ranging study, up to Week 2, all patients had received a single dose of the study drug, allowing for assessment of dose proportionality of itepekimab concentrations independent of the frequency of administration. Concentrations of functional itepekimab concentrations in serum measured at Week 2 appeared approximately dose proportional across the different treatment groups (Table 2). An accumulation of ~ 2- to 4.5-fold was observed in itepekimab trough concentration (C_{trough}) after the last dose when compared with the first dose for itepekimab

q2w (300 mg) or q4w (100 or 300 mg) dosing regimens, while no accumulation was observed for the q8w (30 mg) regimen. The median half-life for itepekimab ranged from 23.1 to 27.8 days between treatment groups. Samples collected in the absorption phase were limited to six patients (enrolled at sites in Japan) for whom the median (range) of t_{max} after the first was 6.98 (2.21–14.0) days and consistent with prior reports.[10]

In the proof-of-concept study, the highest mean C_{trough} of functional itepekimab were observed at Week 16 for both itepekimab alone and itepekimab in combination with dupilumab, indicating the itepekimab 300 mg q2w regimen may require at least 16 weeks to achieve a steady state (Figure 2b; Table 2). An accumulation of approximately threefold was observed for the itepekimab C_{trough} measured after the last dose at Week 16 when compared with after the first dose for itepekimab 300 mg q2w alone and in combination with dupilumab.

Concentration–time profiles for itepekimab in serum were similar between East Asian and non-East Asian patients within each treatment group for both studies (Figure S2A,B).

Itepekimab pharmacodynamics

IL-33 was undetectable at baseline in most patients. Total IL-33 levels in serum increased after administration of itepekimab in both studies, and predominantly represent IL-33 in a complex with itepekimab at post-baseline timepoints (Figure 3a,b). IL-33 levels reached a similar plateau for 300 mg q2w or q4w in the dose-ranging study, indicating that both regimens saturated binding to the IL-33 target in serum (Figure 3a). Total IL-33 increased to a similar level for itepekimab 300 mg q2w with and without dupilumab in the proof-of-concept study (Figure 3b). Mean concentrations of total IL-33 returned to baseline levels by Week 28 for the itepekimab 30 mg q8w group in the proof-of-concept study but remained elevated through Week 36 for all other itepekimab dose groups in both studies. Total IL-33 was unaffected by treatment with a placebo in either study or dupilumab monotherapy in the proof-of-concept study. Concentration–time profiles for total IL-33 in serum were similar between East Asian and non-East Asian patients within each treatment group for both studies (Figure S4A,B).

In the dose-ranging study, reductions in median percent change from baseline in blood eosinophil counts were observed by Week 4 and reached a nadir between weeks 8 and 16; however, there was no apparent relationship between dose and magnitude or time to onset of decreases (Figure 3c). Blood eosinophils returned to baseline by Week 36 for the 30 mg q8w cohort, while reductions were

TABLE 1 Baseline characteristics in the dose-ranging study and proof-of-concept study.

N (%)	Dose-ranging study					Proof-of-concept study			
		Itepekimab							
	Placebo q2w (N=25)	30 mg q8w (N=26)	100 mg q4w (N=26)	300 mg q4w (N=24)	300 mg q2w (N=26)	Placebo q2w (N=50)	Itepekimab 300 mg q2w (N=52)	Dupilumab 300 mg q2w (N=51)	Itepekimab 300 mg and dupilumab 300 mg q2w (N=52)
Age, mean (SD), years	36.6 (14.22)	36.0 (16.41)	37.7 (14.30)	36.2 (12.40)	38.8 (15.44)	34.8 (14.17)	33.3 (12.19)	38.4 (15.89)	32.1 (12.10)
Male sex, n (%)	11 (44.0)	13 (50.0)	14 (53.8)	11 (45.8)	11 (42.3)	32 (64.0)	36 (69.2)	28 (54.9)	30 (57.7)
BMI, mean (SD), kg/m²	27.0 (5.78)	26.3 (4.52)	28.6 (8.40)	26.5 (6.75)	27.3 (4.74)	26.3 (5.30)	26.3 (4.63)	26.2 (6.41)	24.9 (4.78)
Weight, mean (SD), kg	82.2 (26.79)	74.7 (13.66)	82.5 (27.17)	77.7 (23.30)	77.9 (18.14)	76.3 (18.03)	79.6 (17.89)	78.7 (21.82)	74.3 (18.10)
Race, n (%)									
White	13 (52.0)	14 (53.8)	19 (73.1)	11 (45.8)	14 (53.8)	26 (52.0)	29 (55.8)	38 (74.5)	31 (59.6)
Black or African American	3 (12.0)	4 (15.4)	2 (7.7)	3 (12.5)	2 (7.7)	1 (2.0)	6 (11.5)	3 (5.9)	2 (3.8)
Asian	9 (36.0)	8 (30.8)	5 (19.2)	10 (41.7)	10 (38.5)	23 (46.0)	16 (30.8)	10 (19.6)	19 (36.5)
Region, n (%)						0	1 (1.9)	0	0
North America	10 (40.0)	9 (34.6)	9 (34.6)	8 (33.3)	12 (46.2)	8 (16.0)	13 (25.0)	14 (27.5)	11 (21.2)
Asia-Pacific	7 (28.0)	9 (34.6)	5 (19.2)	10 (41.7)	8 (30.8)	19 (38.0)	12 (23.1)	7 (13.7)	15 (28.8)
Eastern Europe	6 (24.0)	6 (23.1)	8 (30.8)	5 (20.8)	4 (15.4)	10 (20.0)	16 (30.8)	17 (33.3)	18 (34.6)
Western Europe	2 (8.0)	2 (7.7)	4 (15.4)	1 (4.2)	2 (7.7)	13 (26.0)	11 (21.2)	13 (25.5)	8 (15.4)
EASI score, mean (SD)	30.3 (11.88)	29.8 (12.00)	33.7 (11.23)	27.7 (10.68)	32.7 (15.13)	28.2 (9.54)	29.9 (13.02)	30.6 (13.86)	29.0 (10.74)
BSA of AD, mean (SD)	48.3 (23.81)	45.9 (22.18)	52.4 (20.17)	43.7 (21.45)	48.9 (21.73)	47.0 (19.18)	45.3 (22.19)	47.9 (23.66)	47.3 (21.00)
Blood eosinophils, 10^9/L									
Mean (SD)	0.59 (0.65)	0.49 (0.37)	0.49 (0.36)	0.41 (0.31)	0.58 (0.39)	0.61 (0.76)	0.47 (0.41)	0.49 (0.43)	0.49 (0.38)
Median (Q1−Q3)	0.4 (0.24−0.75)	0.37 (0.19−0.68)	0.49 (0.19−0.72)	0.31 (0.15−0.71)	0.54 (0.21−0.81)	0.4 (0.26−0.60)	0.43 (0.21−0.58)	0.35 (0.20−0.58)	0.43 (0.21−0.67)

Note: Baseline characteristics presented in the SAF population for the dose-ranging study and proof-of-concept study.

Abbreviations: BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; SAF, safety; SD, standard deviation.

(a)
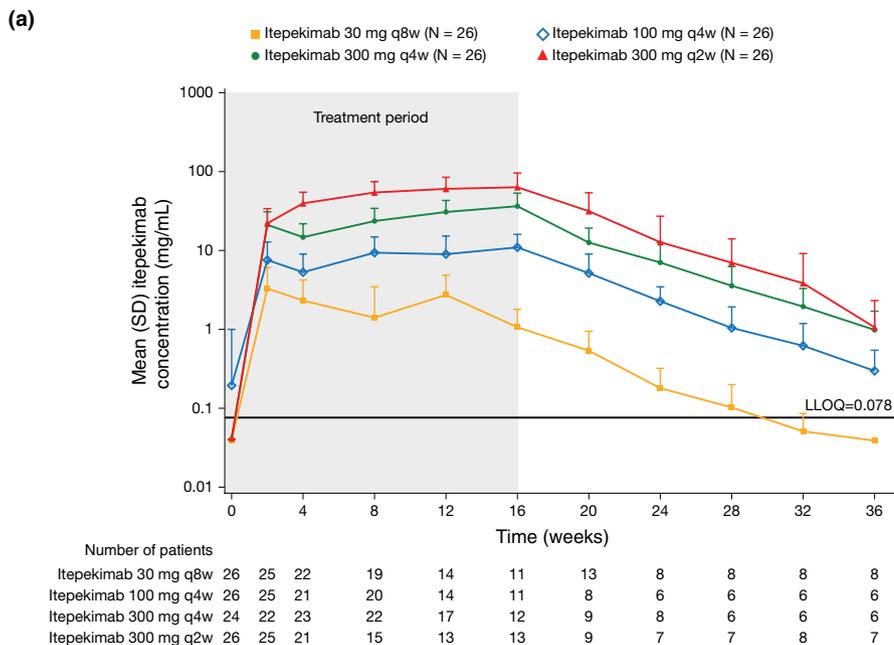
FIGURE 2 Concentration–time profiles of itepekimab during the study period in the (a) dose-ranging study and (b) proof-of-concept study. Concentrations below the lower limit of quantitation (LLOQ) were set to LLOQ/2. Patients who prematurely discontinued treatment were censored at timepoints more than one dosing interval after the last administered dose.

(b)
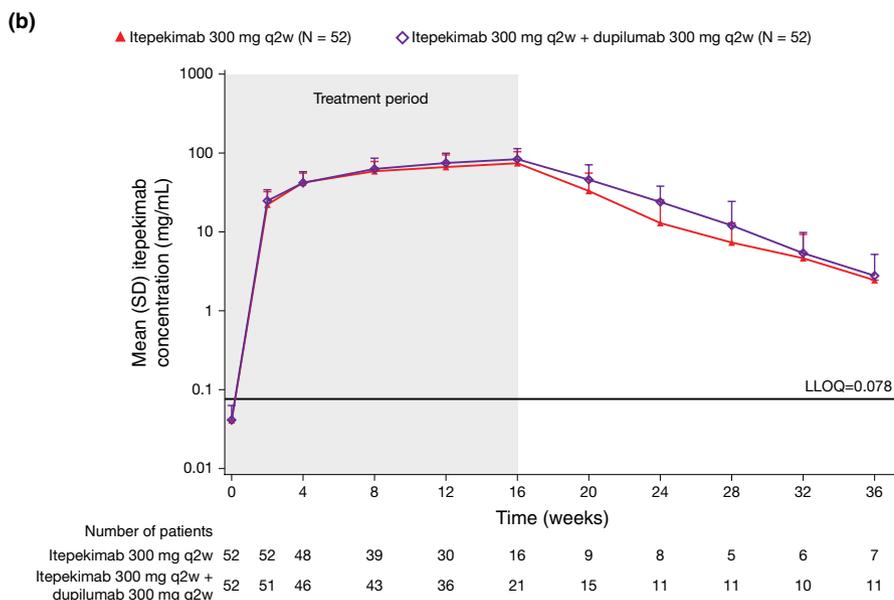
maintained through Week 36 for the higher dose cohorts. Blood eosinophils remained at or above baseline levels for the placebo group throughout the study. In the proof-of-concept study, decreases were observed by Week 4 and sustained to Week 36 for the itepekimab monotherapy and combination with dupilumab treatment arms (Figure 3d). Decreased blood eosinophils were also observed for patients receiving placebo in the proof-of-concept study, but not the dose-ranging study. Observed decreases in patients who received itepekimab were consistent with those previously observed in healthy subjects, patients with asthma, and patients with COPD.[10,11] For patients receiving dupilumab monotherapy, a transient increase in blood eosinophil counts at Week 8, followed by a decline to baseline or

lower, was consistent with prior reports for dupilumab in patients with atopic dermatitis.[27]

Safety

A summary of TEAEs during the study periods of the dose-ranging study and the proof-of-concept study are shown in Table 3.

In the dose-ranging study, the number of patients with at least 1 TEAE reported during the study period was 54.9% (56/102) in the combined itepekimab group and 44.0% in the placebo group (11/25). The higher incidence of nasopharyngitis (10.8% in itepekimab vs. 0% in placebo)

TABLE 2 Pharmacokinetic parameters for itepekimab.

Parameter, mean (SD)	Dose-ranging study				Proof-of-concept study	
	Itepekimab 30 mg q8w (N=26)	Itepekimab 100 mg q4w (N=26)	Itepekimab 300 mg q4w (N=24)	Itepekimab 300 mg q2w (N=26)	Itepekimab 300 mg q2w (N=52)	Itepekimab 300 mg q2w + dupilumab 300 mg q2w (N=52)
C_{trough}/dose, Week 2 (mg/L/mg)	n=25 0.110 (0.0899)	n=25 0.0735 (0.0565)	n=22 0.0712 (0.0328)	n=25 0.0734 (0.0368)	NR	NR
C_{trough}, Week 16 (mg/L)	n=11 1.05 (0.733)	n=11 10.6 (4.91)	n=11 35.2 (17.3)	n=13 60.8 (33.3)	n=16 73.9 (31.4)	n=21 82.4 (33.5)
C_{trough} accumulation ratio	n=6 1.06 (0.588)	n=7 2.09 (0.819)	n=9 3.42 (1.83)	n=8 4.50 (2.86)	n=11 3.24 (1.06)	n=16 2.92 (0.798)
$t_{1/2}$ (days)	n=6 24.6 (5.95)	n=8 27.5 (3.19)	n=8 27.8 (5.99)	n=8 23.1 (5.98)	n=7 27.4 (8.29)	n=12 26.6 (4.64)

Note: Pharmacokinetic parameters presented in the PKAS population. C_{trough}, concentration at the end of the dosing interval; as mean (standard deviation). Accumulation ratio for C_{trough} at Week 16 relative to C_{trough} at Week 8 (q8w), Week 4 (q4w), or Week 2 (q2w); as mean (standard deviation).

Abbreviations: NR, not reported; PKAS, pharmacokinetics; $t_{1/2}$, terminal half-life; as median (range).

and worsening of disease (atopic dermatitis reported in 23.5% in itepekimab vs. 12.0% in placebo) contributed to the higher incidence of all TEAEs between the itepekimab and placebo groups.

Most of the reported TEAEs were mild or moderate in intensity. Overall, there were three treatment-emergent SAE reported (gastroenteritis norovirus and road traffic accident, both in the 300 mg q2w group, and breast cancer in the 300 mg q4w group; Table S3), and none were assessed by the investigator as related to the study drug. There were three patients who permanently discontinued the study drug due to TEAEs (one each from the placebo [type IV hypersensitivity reaction], itepekimab 30 mg q8w [dermatitis atopic], and 300 mg q2w groups [dermatitis atopic]). One death not related to the study drug (road traffic accident) was reported in the itepekimab 300 mg q2w group.

In the proof-of-concept study, the number of patients with at least 1 TEAE reported during the study period was placebo, 54.0% (27/50); itepekimab, 50.0% (26/52); itepekimab plus dupilumab, 53.8% (28/52); and dupilumab, 68.6% (35/51). Most TEAEs were mild or moderate in intensity. Overall, nine treatment-emergent serious adverse events (SAEs) were reported in five patients (Table S4), of which 1 (in the placebo group) was assessed by the investigators to be related to the study drug (hypersensitivity in a patient with multiple pre-existing allergies); the unrelated SAEs were intercranial aneurysm and ruptured cerebral aneurysm [dupilumab group, $N=2$]; acute respiratory failure, encephalopathy, tracheobronchitis, and cerebrovascular accident [itepekimab group, $N=1$]; and a death caused by Goodpasture's syndrome and sepsis [itepekimab plus dupilumab group, $N=1$]. There were five patients who permanently discontinued the study drug due to TEAEs.

No ADAs to itepekimab were observed in either study; additionally, all patients were negative at baseline.

Measures of efficacy

In the dose-ranging study, mean percent change from baseline in EASI score at Week 16 was -33.5% ($n=10$) in placebo, and -57.9% ($n=7$), -52.7% ($n=7$), -80.0% ($n=7$), and -54.0% ($n=9$) in the itepekimab 30 mg q8w, 100 mg q4w, 300 mg q4w, and 300 mg q2w groups, respectively (Figure S3A).

An interim analysis of the proof-of-concept study, focusing on data through 8 weeks of treatment, led to termination of both studies due to a lack of compelling efficacy for itepekimab. At Week 8, mean percent change from baseline in EASI scores were -37.9% ($n=34$) in the placebo group, -44.9% ($n=37$) in the itepekimab monotherapy group, -67.7% ($n=41$) in the dupilumab group, and -63.1% ($n=38$) in the itepekimab plus dupilumab group.
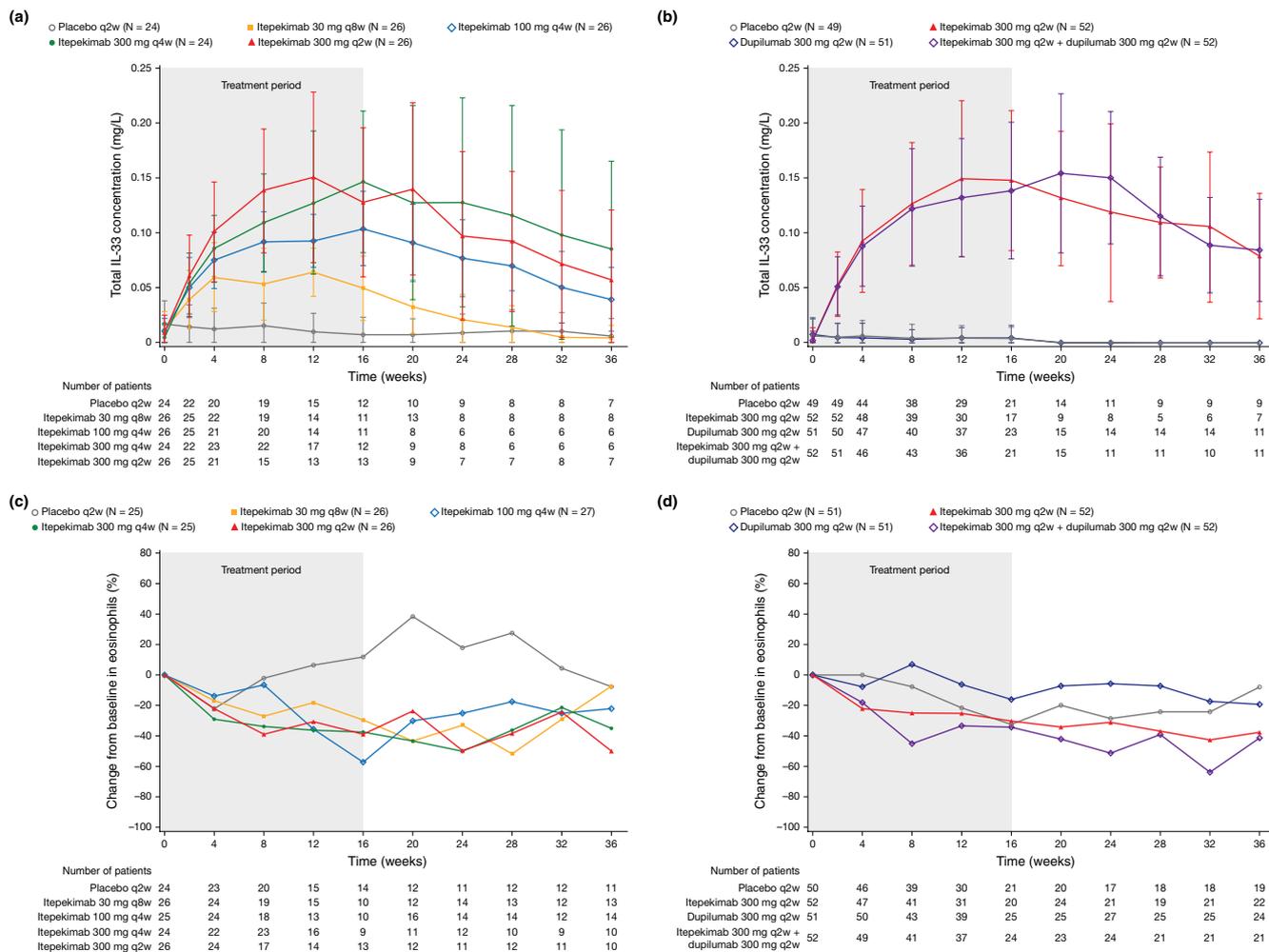
FIGURE 3 Concentration of total IL-33 (a, b) in serum and blood eosinophils (10^9/L) (c, d) during the study period in the dose-ranging study and proof-of-concept study, respectively. For (a, b): Concentrations below the LLOQ were set to zero. Patients who prematurely discontinued treatment were censored at timepoints more than one dosing interval after the last dose. Data are shown as mean (SD). For (c, d): Change from baseline in blood eosinophils presented in the SAF population. Data are shown as median. IQR, interquartile range; LLOQ, lower limit of quantitation; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; SAF, safety.

At Week 16 in the proof-of-concept study, mean percent changes from baseline in EASI score at Week 16 were -52.4% ($n=19$) in the placebo group, -66.6% ($n=14$) in the itepekimab monotherapy group, -77.8% ($n=22$) in the dupilumab group, and -76.9% ($n=20$) in the itepekimab plus dupilumab group (Figure S3B). While the dupilumab arm was consistent with the phase 3 SOLO-1/2 studies of dupilumab in AD, the placebo arm showed a greater increase.[19]

DISCUSSION

Inhibition of type 2 inflammation by blocking Il-4/I-13 signaling via IL-4Rα with dupilumab has been highly effective in AD.[19] Itepekimab monotherapy did not result in meaningful improvements in EASI scores relative to placebo, and did not result in additional clinical improvements in combination with dupilumab over dupilumab monotherapy. Baseline disease characteristics in the patients enrolled in both studies were consistent with patients with moderate-to-severe AD. Baseline blood eosinophils were similar to those seen in prior AD studies,[18,19] and consistently higher than those observed previously in asthma[18] or COPD.[12] Despite minimal improvements in AD efficacy end points, itepekimab 300 mg q2w has demonstrated efficacy in airway diseases of asthma and COPD for which IL-33 is thought to play a more pivotal role.[11,12]

IL-33 and ST2 have a role in the initiation and amplification of type 1 and type 2 inflammation cascades.[1,2] When itepekimab and dupilumab were investigated in a murine model of chronic airway inflammation induced by house dust mite exposure, the combination of both drugs demonstrated superior efficacy to either agent alone in the late phase of mixed type 1 and 2 inflammation.[28] In clinical trials of patients with COPD, another airway disease

TABLE 3 Patients with treatment-emergent adverse events during the study period of the dose-ranging study and the proof-of-concept study.

N (%)	Dose-ranging study					Proof-of-concept study			
	Placebo q2w (N=25)	Itepekimab				Placebo q2w (N=50)	Itepekimab 300 mg q2w (N=52)	Dupilumab 300 mg q2w (N=51)	Itepekimab 300 mg and dupilumab 300 mg q2w (N=52)
		30 mg q8w (N=26)	100 mg q4w (N=26)	300 mg q4w (N=24)	300 mg q2w (N=26)	27 (54.0)	26 (50.0)	35 (68.6)	28 (53.8)
Any TEAE	11 (44.0)	14 (53.8)	14 (53.8)	13 (54.2)	15 (57.7)	1 (2.0)	1 (1.9)	2 (3.9)	1 (1.9)
Any serious TEAE	0	0	0	1 (4.2)	2 (7.7)	2 (4.0)[a]	1 (1.9)[a]	0[a]	2 (3.8)[a]
Any TEAE leading to permanent discontinuation	1 (4.0)[b]	1 (3.8)[b]	0[b]	0[b]	1 (3.8)[b]	0[c]	0[c]	0[c]	1 (1.9)[c]
Any death	0	0	0	0	1 (3.8)	27 (54.0)	26 (50.0)	35 (68.6)	28 (53.8)
TEAE reported by ≥5% of patients in any treatment group by MedDRA Preferred Term									
Dermatitis atopic	3 (12.0)	8 (30.8)	5 (19.2)	5 (20.8)	6 (23.1)	8 (16.0)	5 (9.6)	11 (21.6)	6 (11.5)
Nasopharyngitis	0	2 (7.7)	4 (15.4)	2 (8.3)	3 (11.5)	7 (14.0)	7 (13.5)	8 (15.7)	10 (19.2)
Cellulitis	0	1 (3.8)	0	2 (8.3)	1 (3.8)	1 (2.0)	0	6 (11.8)	1 (1.9)
Toothache	1 (4.0)	0	1 (3.8)	0	2 (7.7)	2 (4.0)	1 (1.9)	3 (5.9)	1 (1.9)
Headache	1 (4.0)	1 (3.8)	0	0	2 (7.7)	2 (4.0)	1 (1.9)	3 (5.9)	1 (1.9)
Edema peripheral	0	2 (7.7)	0	0	1 (3.8)	0	1 (1.9)	2 (3.9)	3 (5.8)
Nausea	1 (4.0)	0	0	2 (8.3)	0	1 (2.0)	0	2 (3.9)	3 (5.8)
Urinary tract infection	2 (8.0)	0	0	1 (4.2)	0	0	0	4 (7.8)	1 (1.9)
Bronchitis	0	0	0	0	2 (7.7)	0	3 (5.8)	1 (2.0)	0

Note: Safety presented in the SAF population for the dose-ranging study and proof-of-concept study. No drug-related treatment-emergent SAEs were reported.

[a]1 (2.0%) drug-related treatment-emergent SAE was reported in the placebo q2w group.

[b]The number of patients discontinuing treatment due to TEAE was as follows: in the placebo group, 1 (4%) patient discontinued treatment due to a type 4 hypersensitivity reaction; in the itepekimab 30 mg q8w group, 1 (3.8%) discontinued treatment due to atopic dermatitis; no patients discontinued from the itepekimab 100 mg q4w or the 300 mg q4w groups; and in the itepekimab 300 mg q2w group, 1 (2%) patient discontinued due to atopic dermatitis. MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SAE, serious adverse event; SAF, safety; TEAE, treatment-emergent adverse event.

[c]The number of patients discontinuing treatment due to TEAE was as follows: in the placebo group, 1 (2%) patient discontinued treatment due to an abscess, and 1 (2%) due to hypersensitivity; in the itepekimab 300 mg q2w group, 1 (1.9%) patient discontinued treatment due to atopic dermatitis; no patients from the dupilumab 300 mg q2w group discontinued; and in the itepekimab 300 mg and dupilumab 300 mg q4w group, 1 patient (1.9%) discontinued treatment due to sepsis and Goodpasture's syndrome, and 1 (1.9%) due to alanine aminotransferase increasing and aspartate aminotransferase increasing.

characterized by mixed inflammation,[29] reduced rates of acute exacerbations of COPD and improvement in lung function have been observed for patients who are former smokers receiving itepekimab,[12] and patients with a type 2 phenotype characterized by blood eosinophil counts >300 cells/μL receiving dupilumab.[30]

Both clinical studies of itepekimab in patients with AD were terminated following an unblinded interim assessment of data through Week 8 from the proof-of-concept study, where it was determined that the efficacy of itepekimab was not sufficient to continue the studies. Although trough concentrations of itepekimab had not achieved steady state by Week 8 and greater improvement in signs and symptoms of AD through Week 16 was possible, it was deemed that a therapy requiring such an extended onset of benefit was not favorable for the treatment of patients with moderate-to-severe AD. Prior studies using anti-IL-33 drugs, including LY3375880 and etokimab, have also shown a lack of efficacy in AD, and a higher itepekimab dose regimen was considered unlikely to change the outcome.[31,32] Although patients with AD exhibit an increased expression of IL-33 and ST2 in response to allergen exposure and increased expression of IL-33 in AD lesions,[33] the lack of clinical efficacy of anti-IL-33 drugs suggests that IL-33 may not be a key pathogenic driver of AD. The role of anti-IL-33 therapies, being upstream of IL-13, may be largely redundant with the effects of dupilumab in predominantly type 2 inflammatory conditions like AD.

Although these two studies were prematurely terminated, study integrity and blinding to the sites, operational teams, and study patients were maintained through last-patient last-visit of the follow-up period. Over 100 patients completed the treatment period as originally planned in either study and provided a large amount of pharmacokinetic and/or pharmacodynamic data. The inclusion of patients who prematurely discontinued the study drug with censoring following discontinuation allowed for further enrichment of these datasets. A placebo control group was used in the proof-of-concept study as the study, was designed to mirror the inclusion and exclusion criteria of the two-placebo-controlled, phase 3 dupilumab pivotal trials SOLO 1/SOLO2,[19] to enable a comparison of the itepekimab efficacy to the historical data. Rescue drugs were available to enrolled patients if the patient's AD signs and symptoms became unmanageable.

In these phase II studies in adults with moderate-to-severe AD, itepekimab demonstrated both linear and dose-proportional pharmacokinetics that were unaffected by coadministration with dupilumab. Pharmacodynamic assessments indicated itepekimab successfully engaged the target, with downstream impacts evident in reduced blood eosinophil counts. The pattern of increasing total IL-33 concentrations following itepekimab treatment is consistent with prolonged circulation of the short-lived IL-33 alarmin as a complex with itepekimab. Similar peak concentrations of total IL-33 were observed in patients receiving itepekimab 300 mg q2w and q4w, suggesting equivalent saturating of binding in serum.

A frequent concern expressed by global health authorities is potential differences in the pharmacokinetics of investigational drugs between East Asian and Western patients, which may result from demographic, genetic, or epigenetic differences between these populations. This risk is lower for mAbs that are not metabolized and have limited tissue penetration than for small molecule drugs, especially when PK is linear and there is less potential for differences in target expression between ethnic groups to impact PK.[34] The concentration–time profiles of itepekimab and total IL-33 were similar for patients with AD from East Asian and non-East Asian (North American and European) subgroups, and supported the inclusion of patients with COPD from East Asian countries in global phase III studies without dose adjustment.

Itepekimab was generally well tolerated in these studies, adding to the accumulating evidence of its acceptable safety profile.[10–12] No treatment-emergent ADAs to itepekimab were observed in either study. Safety in patients treated with dupilumab was consistent with the known safety profile in patients with moderate-to-severe AD.[19]

In conclusion, these studies demonstrate that both itepekimab monotherapy and the combination of itepekimab and dupilumab were well tolerated in adults with moderate-to-severe AD, with no ADA response seen to itepekimab. The pharmacokinetics and pharmacodynamics of itepekimab were consistent with expectations from prior studies. A lack of clinical efficacy in an interim analysis led to the termination of these studies, and suggests that IL-33 may not be a primary pathogenic driver in chronic atopic dermatitis.

CONFLICT OF INTEREST STATEMENT
M.P.K., M.A.K., E.A., J.D.D., and A.R. are employees and shareholders of Regeneron Pharmaceuticals Inc. X.Z., M.C.N., and A.S. are former employees and shareholders of Regeneron Pharmaceuticals Inc. E.G.-Y. is a consultant for AbbVie, Almirall, Amgen, AnaptysBio, Apogee Therapeutics, Apollo Therapeutics Ltd., Artax Biopharma Inc., AstraZeneca, Bristol Myers Squibb, Boehringer Ingelhiem, Cara Therapeutics, Centrexion Therapeutics Corporation, Connect Biopharma, Eli Lilly, Enveda Biosciences, Escient Pharmaceuticals, Inc., Fairmount Funds Management LLC, FL2022-001, Inc., Galderma, Gate Bio, Google Ventures, GSK, Horizon Therapeutics USA, Inc., Incyte, Inmagene, Janssen, Japan Tobacco, Jasper Therapeutics, Kyowa Kirin, LEO Pharma, Merck, Nektar Therapeutics, Novartis, NUMAB Therapeutics AG, OrbiMed Advisors LLC, Pfizer, Pharmaxis Ltd, Pioneering Medicines VII, Inc., Proteologix US Inc., RAPT, Regeneron Pharmaceuticals Inc., Ribon Therapeutics, Inc., Sanofi, SATO, Schrödinger, Inc., SPARC, Teva Branded Pharmaceutical Products R&D, Inc., UCB; and has received research funds from Amgen, AnaptysBio, Aslan, Bristol Myers Squibb, Boehringer Ingelheim, Cara Therapeutics, Concert, GSK, Incyte, Janssen, Kyowa Kirin, LEO Pharma, Pfizer, RAPT, Regeneron Pharmaceuticals Inc., Sanofi, UCB. M.J.C. has been an investigator for Atopix, Galapagos Pharmaceutical Company, Hyphens Pharma, Johnson & Johnson, Kymab, La Roche-Posay, LEO Pharma, L'Oréal, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi; and is an advisory board member/consultant/speaker for Astellas, Atopix, Boots, Dermavant, Galapagos Pharmaceutical Company, Galderma, Hyphens Pharma, Johnson & Johnson, Kymab, La Roche-Posay, LEO Pharma, L'Oréal, Menlo Therapeutics, Novartis, Oxagen, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron Pharmaceuticals Inc., Sanofi. M.W. reports honoraria and/or consulting fees from AbbVie, Aimmune Therapeutics, ALK-Abelló, Allergopharma, Almirall, Amgen, Biotest, Boehringer Ingelheim, DBV Technologies, Genzyme, Kymab, LEO Pharma, Eli Lilly, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, Stallergenes Greer, Worg Pharmaceutics. D.-H.N. declares no conflict of interest for this work. M.K.R. and S.H. are prior employees and shareholders of Regeneron Pharmaceuticals Inc. H.G. and C.R.X. are employees of Sanofi, and may hold stock and/or stock options in the company.

ORCID
Matthew P. Kosloski https://orcid.org/0000-0002-6642-2439

Emma Guttman-Yassky https://orcid.org/0000-0002-9363-324X
Michael J. Cork https://orcid.org/0000-0003-4428-2428
Dong-Ho Nahm https://orcid.org/0000-0001-5253-6577
Hélène Goulaouic https://orcid.org/0009-0003-4713-0216
John D. Davis https://orcid.org/0000-0001-6282-1670

REFERENCES

1. Cayrol C, Girard JP. Interleukin-33 (IL-33): a nuclear cytokine from the IL-1 family. *Immunol Rev*. 2018;281(1):154-168.
2. Allinne J, Scott G, Lim WK, et al. IL-33 blockade affects mediators of persistence and exacerbation in a model of chronic airway inflammation. *J Allergy Clin Immunol*. 2019;144(6):1624-1637.e10.
3. Brandt EB, Sivaprasad U. Th2 cytokines and atopic dermatitis. *J Clin Cell Immunol*. 2011;2(3):110.
4. Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130(6):1344-1354.
5. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev*. 2011;242(1):233-246.
6. Williams MR, Gallo RL. The role of the skin microbiome in atopic dermatitis. *Curr Allergy Asthma Rep*. 2015;15(11):65.
7. Imai Y. Interleukin-33 in atopic dermatitis. *J Dermatol Sci*. 2019;96(1):2-7.
8. MacDonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci USA*. 2014;111(14):5147-5152.
9. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci USA*. 2014;111(14):5153-5158.
10. Kosloski MP, Kalliolias GD, Xu CR, et al. Pharmacokinetics and pharmacodynamics of itepekimab in healthy adults and patients with asthma: phase I first-in-human and first-in-patient trials. *Clin Transl Sci*. 2022;15(2):384-395.
11. Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and safety of itepekimab in patients with moderate-to-severe asthma. *N Engl J Med*. 2021;385(18):1656-1668.
12. Rabe KF, Celli BR, Wechsler ME, et al. Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial. *Lancet Respir Med*. 2021;9(11):1288-1298.
13. Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract*. 2017;5(6):1572-1581.e3.
14. European Medicines Agency. DUPIXENT® (dupilumab). Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf. Accessed November 10, 2023.
15. US Food and Drug Administration. DUPIXENT® (dupilumab). Highlights of Prescribing Information. https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf. Accessed November 10, 2023.
16. He H, Olesen CM, Pavel AB, et al. Tape-strip proteomic profiling of atopic dermatitis on dupilumab identifies minimally invasive biomarkers. *Front Immunol*. 2020;11:1768.

17. Guttman-Yassky E, Bissonnette R, Ungar B, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2019;143(1):155-172.

18. Hamilton JD, Harel S, Swanson BN, et al. Dupilumab suppresses type 2 inflammatory biomarkers across multiple atopic, allergic diseases. *Clin Exp Allergy.* 2021;51:915-931.

19. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* 2016;375(24):2335-2348.

20. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet.* 2016;387(10013):40-52.

21. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10086):2287-2303.

22. Ramirez-Carrozzi V, Sambandam A, Zhou M, et al. Combined blockade of the IL-13 and IL-33 pathways leads to a greater inhibition of type 2 inflammation over inhibition of either pathway alone. *J Allergy Clin Immunol.* 2017;139(2):705-708.e6.

23. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma [published correction appears in N Engl J med. 2019 May 23;380(21):2082]. *N Engl J Med.* 2017;377:936-946.

24. Simpson EL, Parnes JR, She D, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: a randomized phase 2a clinical trial. *J Am Acad Dermatol.* 2019;80(4):1013-1021.

25. Chen YL, Gutowska-Owsiak D, Hardman CS, et al. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. *Sci Transl Med.* 2019;11(515):eaax2945.

26. ClinicalTrials.gov. NCT03533751. Efficacy, safety, and pharmacokinetic profile of etokimab (ANB020) in adult participants with moderate-to-severe atopic dermatitis (ATLAS) – Results Overview. https://www.clinicaltrials.gov/study/NCT03533751?term=NCT03533751&rank=1&tab=results. Accessed November 10, 2023.

27. Wechsler ME, Klion AD, Paggiaro P, et al. Effect of dupilumab on blood eosinophil counts in patients with asthma, chronic rhinosinusitis with nasal polyps atopic dermatitis, or eosinophilic esophagitis. *J Allergy Clin Immunol Pract.* 2022;10(10):2695-2709.

28. Asrat S, Scott G, Allinne J, et al. IL-33 and IL-4Rα blockade impact distinct and overlapping inflammatory mediators of airway disease. *Eur Respir J.* 2022;60(66):477.

29. King PT. Inflammation in chronic obstructive pulmonary disease and its role in cardiovascular disease and lung cancer. *Clin Transl Med.* 2015;4(1):68.

30. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med.* 2023;389(3):205-214.

31. Laquer V, Parra V, Lacour JP, et al. Interleukin-33 antibody failed to demonstrate benefit in a phase II, double-blind, randomized, placebo-controlled study in adult patients with moderate-to-severe atopic dermatitis. *Br J Dermatol.* 2022;187(4):599-602.

32. AnaptysBio. AnaptysBio reports etokimab atlas phase 2B clinical trial in moderate-to-severe atopic dermatitis fails to meet primary endpoint. https://ir.anaptysbio.com/news-releases/news-release-details/anaptysbio-reports-etokimab-atlas-phase-2b-clinical-trial. Accessed May 8, 2024.

33. Savinko T, Matikainen S, Saarialho-Kere U, et al. IL-33 and ST2 in atopic dermatitis: expression profiles and modulation by triggering factors. *J Invest Dermatol.* 2012;132(5):1392-1400.

34. Chiba K, Yoshitsugu H, Kyosaka Y, et al. A comprehensive review of the pharmacokinetics of approved therapeutic monoclonal antibodies in Japan: are Japanese phase I studies still needed? *J Clin Pharmacol.* 2014;54(5):483-494.

SUPPORTING INFORMATION

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