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Safety, Pharmacokinetics, and Immunogenicity of Astegolimab, an Anti-ST2 Monoclonal Antibody, in Randomized, Phase I Clinical Studies

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ABSTRACT

Astegolimab, a fully human immunoglobulin G2 monoclonal antibody, binds with high affinity to ST2, the interleukin-33 receptor, thereby blocking ST2/interleukin-33 binding and subsequent inflammatory cascades involved in inflammatory diseases. Here, we present three randomized, double-blind, placebo-controlled, Phase I studies evaluating the safety, tolerability, pharmacokinetics, and immunogenicity of single-ascending doses of astegolimab in healthy participants and patients with mild atopic asthma (NCT01928368), multiple-ascending doses in healthy participants (NCT02170337), and single-ascending doses in healthy Japanese and White adults. Overall, 152 participants were enrolled, randomized, and treated with single- or multiple-ascending doses of astegolimab ($n = 112$) or placebo ($n = 40$) subcutaneously (2.1–560 mg) or intravenously (210 or 700 mg). No deaths, serious adverse events, or discontinuations due to adverse events occurred during the studies. No clinically meaningful differences in incidence of TEAEs were observed between treatment arms. Pharmacokinetic exposure increased more than dose proportionally over 2.1–420 mg for single-ascending doses but were approximately dose proportional for single- and multiple-ascending doses ≥ 70 mg following subcutaneous administration. No pharmacokinetic differences were observed based on ethnicity between Japanese and White participants following body weight adjustments. Incidence of antidrug antibodies to astegolimab in healthy participants in the single- and multiple-ascending dose studies was 14%–23% and 33%–50% for subcutaneous and intravenous administration, respectively. Astegolimab was well tolerated in these Phase I studies with no safety concerns identified. Thus, further assessment of astegolimab in targeted patient populations was justified; the Phase IIb ALIENTO and Phase III ARNASA trials in patients with chronic obstructive pulmonary disease are ongoing.

Prior Presentation: Data from the subcutaneous dosing of healthy volunteers in the SAD and MAD studies have been presented in poster form at the European Respiratory Society (ERS) Congress, Vienna, Austria, September 7–11, 2024. Additionally, a secondary analysis (Sperinde et al. *Bioanalysis*. 2023; 15:1305–1314) used data from one of the Phase I trials (NCT02170337) to investigate the impact of assay format and target-mediated drug disposition on the nonlinear pharmacokinetics of astegolimab. The current manuscript reports the full results of that Phase I trial and two other Phase I trials.

Study Highlights

- What is the current knowledge on the topic?
  - There is an urgent unmet need to develop new therapies for chronic obstructive pulmonary disease (COPD) to prevent acute exacerbations, slow disease progression, and improve patient outcomes. Blocking the initiation of ST2/IL-33 pathway signaling has been proposed as a strategy for the treatment of inflammatory airway disorders as this pathway promotes innate and adaptive immune inflammatory responses. Astegolimab, a fully human IgG2 monoclonal antibody, binds with high affinity to ST2, thereby blocking the binding of IL-33 and the subsequent inflammatory cascade associated with COPD.
- What question did this study address?
  - Whether the safety, tolerability, pharmacokinetics (PK), and immunogenicity of single and repeated doses of astegolimab in healthy participants and patients with mild atopic asthma are acceptable.
- What does this study add to our knowledge?
  - These Phase I studies demonstrate that astegolimab was well tolerated with no safety concerns identified. In healthy participants, astegolimab exposure increased approximately dose proportionally in the dose range of ≥ 70 mg for single and multiple dosing but was greater than dose proportional in the overall range of 2.1–420 mg with single dosing.
- How might this change clinical pharmacology or translational science?
  - The results of Phase I studies demonstrate that astegolimab has a well-tolerated safety profile that justifies further assessment in targeted patient populations. PK data from these Phase I studies informed the dosing of subsequent astegolimab trials, and following the now completed Phase II trials, astegolimab is being investigated in patients with COPD who have a history of frequent exacerbations in the Phase IIb ALIENTO (NCT05037929) and Phase III ARNASA (NCT05595642) clinical trials.

1 | Introduction

ST2 (IL1R1 or interleukin 1 receptor 1) is a transmembrane receptor that is expressed on the surface of many immune cells and is the main receptor for interleukin (IL)-33 [1, 2]. IL-33 is an alarmin cytokine that activates the immune system and is involved in a broad range of inflammatory responses when passively released from damaged barrier cells such as the pulmonary vascular endothelium and airway epithelium [1–3]. ST2 is expressed across a broad range of immune cell types associated with neutrophilic (type 1 and type 3) and eosinophilic (type 2) inflammation [1–4]. Thus, the activation of the ST2/IL-33 signaling pathway drives multiple inflammatory responses including both neutrophilic and eosinophilic inflammation [1, 2].

Typically, the binding of membrane-bound ST2 with free IL-33 is tightly regulated by soluble ST2 (sST2), a decoy receptor that sequesters free IL-33 and can prevent the subsequent inflammatory cascade [1, 3]. In spite of this, the ST2/IL-33 pathway has been implicated in multiple inflammatory-mediated disorders, such as chronic obstructive pulmonary disease (COPD), asthma, and rheumatoid arthritis [2, 5, 6]. In COPD, IL-33 is involved in airway remodeling and increased expression within lung tissue has been negatively correlated with lung function [2, 5]. Additionally, IL-33 plasma levels have been shown to positively correlate with COPD severity and frequency of acute exacerbations of COPD [5]. While these collective results could make IL-33 a potential biomarker, it may often be undetectable, likely due to high levels of circulating sST2 [7]. Higher levels of sST2 have been observed in patients with COPD compared with healthy nonsmokers, and were positively correlated with disease severity [7]. In the same prospective cohort study, the concentration of sST2 increased significantly during exacerbations, but returned to baseline at follow-up, and sST2 was established as a strong, independent predictor of all-cause mortality [7].

Since new therapies for COPD are urgently needed to prevent exacerbations, slow disease progression, and improve patient outcomes [8], the ST2/IL-33 pathway has become a promising potential therapeutic target for inflammatory-mediated disorders, and blocking its initiation has been proposed as a strategy for the treatment of COPD and other inflammatory airway diseases [1, 9]. Astegolimab, a fully human immunoglobulin (Ig) G2 monoclonal antibody, binds with high affinity to ST2, thereby blocking the binding of IL-33 and subsequent downstream signaling [9, 10]. In Phase II trials, astegolimab demonstrated an adequate safety profile with no safety concerns identified in patients with severe asthma, moderate-to-severe atopic dermatitis, moderate-to-very-severe COPD, or hospitalized with severe coronavirus disease 2019 (COVID-19) pneumonia [9–12]. The efficacy and safety of astegolimab are currently being evaluated in patients with COPD who have a history of frequent exacerbations in the pivotal Phase IIb ALIENTO (NCT05037929) and Phase III ARNASA (NCT05595642) trials, and the long-term safety of astegolimab is also being evaluated in the Phase III ALNASA open-label extension study (NCT05878769). Here, we report three Phase I studies that evaluated the safety, tolerability, pharmacokinetics (PK), and immunogenicity of single and multiple doses of astegolimab.

2 | Materials and Methods

2.1 | Study Designs and Populations

Astegolimab was assessed in three randomized, double-blind, placebo-controlled, Phase I studies conducted across multiple centers in the United States (Figure 1; Figure S1). The protocols and informed consent forms were reviewed and approved by the Institutional Review Board (IRB) for each study center before the recruitment of participants into each study. The IRB names, protocol approval numbers, and dates are listed in Table S1. All studies were conducted in accordance with the principles of the Food and Drug Administration and the International Council for Harmonisation Guidance for Good Clinical Practice.

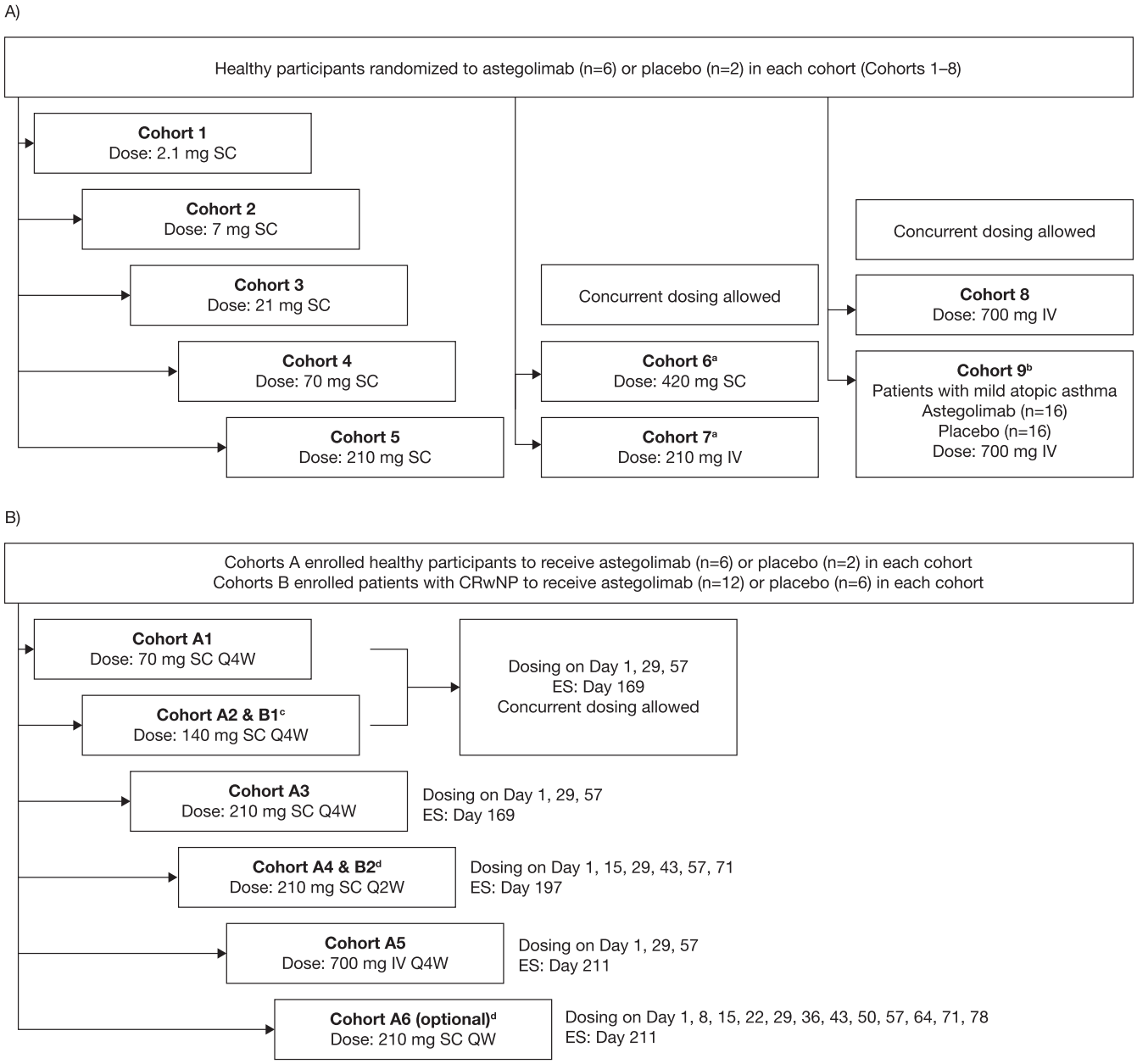

FIGURE 1 | Astegolimab Phase I (A) SAD and (B) MAD study designs. [a]Where Cohorts 6 and 7 were open to enrollment at the same site, enrollment into Cohort 6 took precedence. [b]Cohort 9 enrolled two patients randomized to astegolimab and four patients to placebo; it was the only cohort with a variation to the planned enrollment. [c]Cohort B1 only enrolled one patient. [d]Cohorts A6 and B2 were not conducted because of early termination of the study. CRwNP, chronic rhinosinusitis with nasal polyps; ES, end of study; IV, intravenous; MAD, multiple-ascending dose; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; SAD, single-ascending dose; SC, subcutaneous.

Full eligibility criteria for each trial are in Table S2. A summary of each trial is given below.

The Phase Ia single-ascending dose (SAD) study (ClinicalTrials.gov identifier: NCT01928368) was conducted in healthy participants and patients with mild atopic asthma. Healthy participants received a single subcutaneous (SC; 2.1–420 mg) or intravenous (IV; 210 or 700 mg) dose of astegolimab or placebo, and patients with mild atopic asthma received astegolimab 700 mg IV or placebo (Figure 1A). The randomization ratio was 3:1 astegolimab:placebo in healthy participants and 1:1 in patients with mild atopic asthma. Eligible participants were aged ≥18 and ≤55 years with a body mass index (BMI) ≥18 and ≤32 kg/m^2; patients with mild atopic asthma had a documented history of stable disease within 2 years of screening as defined by the American Thoracic Society/European Respiratory Society statement [13].

The Phase Ib two-part multiple-ascending dose (MAD) study (ClinicalTrials.gov identifier: NCT02170337) was conducted in healthy participants and patients with chronic rhinosinusitis with nasal polyps (CRwNP). In Part A, healthy participants received multiple doses of SC (70, 140, or 210 mg every 4 weeks [Q4W] or 210 mg every 2 weeks [Q2W]/every week [QW]) or IV (700 mg Q4W) astegolimab or placebo (Figure 1B). In Part B, patients with CRwNP received SC (140 mg Q4W or 210 mg Q2W)

astegolimab or placebo. Participants were randomized to astegolimab or placebo in a 3:1 ratio in Part A and 2:1 in Part B. Eligible healthy participants (Part A) were aged ≥18 and ≤45 years with a BMI ≥18 and ≤32 kg/m^2 and eligible patients with CRwNP (Part B) were aged ≥18 and ≤65 years with bilateral nasal polyps grade ≥2 at screening and baseline.

In the Phase I SAD study in healthy Japanese and White participants, participants received a single SC dose (70–560 mg and 210 mg, respectively) of astegolimab or placebo (Figure S1). Participants were randomized to astegolimab or placebo in a 3:1 ratio. Eligible participants were aged ≥18 and ≤45 years, current nonsmokers (no use of nicotine/tobacco-containing products within 6 months) with a BMI ≥18 and ≤32 kg/m^2. Japanese participants were first, second, or third generation with at least four first-generation participants in each Japanese cohort.

In all three studies, Amgen Biostatistics generated the randomization lists with block permutation and provided them to the unblinded pharmacist at each study site, where the participants were enrolled according to the randomization sequence. All other study site and Amgen staff remained blinded, with unblinding prior to database lock allowed only for urgent safety issues. Data reviews for dose escalation were done in a blinded fashion.

2.2 | Endpoints and Assessments

In the SAD and MAD studies, the primary objective was safety, tolerability, and immunogenicity, as assessed by the incidence of treatment-emergent adverse events (TEAEs) graded per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, vital signs, physical examinations, laboratory safety tests, 12-lead electrocardiograms (ECGs), and incidence of anti-drug antibodies (ADAs). Secondary objectives included serum PK parameters of astegolimab.

In the Japanese SAD study, the primary objectives were (1) safety, tolerability, and immunogenicity, as assessed by the incidence of TEAEs, vital signs, physical examinations, laboratory safety tests, and incidence of ADAs, and (2) serum PK parameters of astegolimab. The secondary objective was to compare the safety, tolerability, and PK of astegolimab in Japanese and White participants.

sST2 concentrations in serum samples were also evaluated. Sampling timepoints for PK and sST2 measurements are summarized in Table S3.

2.3 | Pharmacokinetic Analyses

The PK parameters calculated for the three Phase I studies are listed in Appendix 1.1. Serum samples were obtained for all participants, and the determination of free astegolimab concentrations in serum was done using the electrochemiluminescent method described previously [14]. The immunoassay consisted of a sandwich format that utilized two anti-idiotype antibodies to quantify the antibody drug in participant serum, and therefore detected free drug. Actual dosing and collection times were used in the analysis. Nominal sampling times were used for presenting data in graphs and tables. Serum concentrations below the lower limit of quantification (0.100 μg/mL for astegolimab) were set to 0 before data analysis.

2.4 | Immunogenicity Evaluations

The methods for immunogenicity evaluations have been previously described [14]. Briefly, an electrochemiluminescence-based immunoassay was utilized on the Meso Scale Discovery platform that followed a two-tiered assay approach consisting of a screening assay and a confirmatory assay. These assays used two conjugated reagents to bridge antibodies directed against astegolimab: biotinylated astegolimab and ruthenylated astegolimab. Samples with a signal-to-noise value greater than the assay cut point in the screening assay were then tested in the confirmatory assay to confirm the specificity of the response. Screening assay sensitivity was 8 ng/mL; 125 ng/mL of positive control could tolerate 50 μg/mL of astegolimab. ADAs were defined as transient when the participant's last tested time point within the study period resulted in a negative ADA result.

Confirmed ADA-positive samples were analyzed in a competitive binding assay for the detection of neutralizing ADAs against astegolimab.

2.5 | Soluble ST2 Analyses

Serum sST2 concentrations were obtained from the blood samples collected for PK analysis. The sST2 assay used here has been previously described [14] and is briefly summarized in Appendix 1.2.

2.6 | Statistical Analyses

Planned sample sizes were 96 participants in the SAD study, including 32 participants with mild atopic asthma; 84 participants in the MAD study, including 36 participants with CRwNP; and 40 participants in the Japanese SAD study. Sample sizes were based on practical considerations and the ability to detect differences in area under the concentration–time curve (AUC) or incidence of AEs. Detailed sample size considerations are listed in Appendix 1.3.

The safety analysis set consisted of all participants who received at least one dose of astegolimab or placebo. The PK analysis set consisted of all participants who received astegolimab and for whom at least one PK sample was collected. The PK parameter analysis set consisted of all participants who received astegolimab and for whom PK parameters could be adequately estimated. The immunogenicity analysis set consisted of all participants with at least one post-dose ADA assessment.

Categorical data were summarized by the number and percentage of participants in each category. Continuous variables were summarized using descriptive statistics. Serum astegolimab concentration–time data were analyzed by noncompartmental methods using Phoenix WinNonlin v.6.4 (Pharsight,

St. Louis, MO, USA). All original graphs and summary statistic values were prepared using Phoenix WinNonlin or SAS v. 9.3 (SAS Institute Inc., Cary, NC). Methods for a weight-adjusted PK analysis in the Japanese SAD study are described in Appendix 1.4.

3 | Results

3.1 | Participants

The baseline characteristics are shown in Table 1. Demographics were generally well balanced between treatment arms for each study cohort. The mean age was 27–36 years, and all participants were male except four in the SAD study.

In the SAD study, 70 participants were enrolled and randomized (64 healthy participants, six patients with mild atopic asthma) between August 2013 and November 2015 (Figure S2A). Of the 64 healthy participants, six each in cohorts 1–6 received a single 2.1, 7, 21, 70, 210, or 420 mg SC dose of astegolimab, two each in cohorts 1–6 received SC placebo, six participants each in cohorts 7 and 8 received a 210 or 700 mg IV dose of astegolimab, and four participants received IV placebo. Of the six patients with mild atopic asthma, two received 700 mg IV astegolimab, and four received placebo. Enrollment of patients with mild atopic asthma was terminated early due to administrative considerations, with no safety concerns identified, and did not reach the target enrollment of 32 patients.

In the MAD study, 40 healthy participants were enrolled and randomized between July 2014 and December 2015 (Figure S2B). Of those, 30 participants received 70, 140, or 210 mg SC Q4W, 210 mg SC Q2W, or 700 mg IV Q4W doses of astegolimab ($n = 6$ each) and 10 participants received SC ($n = 8$) or IV ($n = 2$) placebo. Across all cohorts, one (4.2%) participant in the 140-mg Q4W SC astegolimab arm and one (12.5%) participant receiving SC placebo did not complete treatment. No participants were enrolled in the 210 mg SC QW in the healthy participants cohort and 210 mg SC Q2W in the patients with CRwNP cohort, due to early study termination for administrative considerations with no safety concerns identified (Figure 1B). Since only one patient with CRwNP was enrolled (SC Q4W 140 mg) prior to early study termination, the results for the CRwNP cohort are not presented in this manuscript.

In the Japanese SAD study, 41 participants were enrolled and randomized (33 Japanese participants, eight White participants) between October 2014 and August 2015 (Figure S2C). Of the 33 Japanese participants, 25 received a single 70 ($n = 6$), 210 ($n = 6$), 420 ($n = 7$), or 560 mg ($n = 6$) SC dose of astegolimab, and eight participants received placebo. Of the eight White participants, six received 210 mg SC astegolimab, and two received placebo.

3.2 | Safety

A summary of TEAEs in healthy participants in the SAD and MAD studies is presented in Table 2. A summary of TEAEs in patients with mild atopic asthma in the SAD study and healthy participants in the Japanese SAD study is presented in Table S4. No deaths, serious AEs, or discontinuations due to AEs occurred during any of the studies. No grade ≥ 3 AEs were reported in the SAD and Japanese SAD studies. In the MAD study, three participants experienced grade ≥ 3 AEs unrelated to astegolimab: grade 4 increased blood creatine phosphokinase (SC: 70 mg Q4W, 1 participant [16.7%]; 140 mg Q4W, 1 participant [16.7%]) and grade 3 syncope (IV 700 mg Q4W, 1 participant [16.7%]). No clinically meaningful differences in the incidence of TEAEs were observed between the astegolimab and placebo arms. Furthermore, no dose dependence in the incidence of AEs was observed in the SAD study (SC: 2.1 mg, 16.7%; 7 mg, 66.7%; 21 mg, 66.7%; 70 mg, 66.7%; 210 mg, 50.0%; 420 mg, 66.7%; IV: 210 mg, 16.7%; 700 mg, 50%) or MAD study (SC: 70 mg Q4W, 83.3%; 140 mg Q4W, 33.3%; 210 mg Q4W, 33.3%; 210 mg Q2W, 33.3%). In healthy participants, upper respiratory tract infection was the most common AE in both the astegolimab and placebo arms (SAD: astegolimab, 12.5%; placebo, 12.5%; MAD: astegolimab, 16.7%; placebo, 10%; Japanese SAD: astegolimab, 0%, placebo, 20%). No cardiac AEs were reported in any of the studies. Complete listings of all AEs are presented in Table S5.

3.3 | Pharmacokinetics

A concentration–time plot for the SAD study is shown in Figure 2A. Table 3 and Table S6 summarize the PK parameters. PK data for SC dosing cohorts of the SAD study have been previously reported [14]. Mean bioavailability after a single 210 mg SC dose in healthy participants was estimated to be 60%. Subcutaneous astegolimab demonstrated a nonlinear PK profile where maximum observed drug concentration (C_{max}) and area under the concentration–time curve from time 0 to time of last quantifiable concentration (AUC_{last}) increased more than dose proportionally over 2.1–420 mg but were approximately dose proportional for ≥ 70 mg SC. In addition, other PK parameters such as clearance and terminal half-life ($t_{1/2,z}$) showed dose-dependent trends, where slower clearance and longer $t_{1/2,z}$ were generally observed at higher doses, indicating target-mediated drug disposition (TMDD) was involved. Figure S3 shows the concentration–time plot for patients with mild atopic asthma in the SAD study. While astegolimab exposure in two patients with mild atopic asthma was determined, a comparison to astegolimab exposure in healthy participants receiving the same dose was not conducted due to the limited number of participants with mild atopic asthma.

A concentration–time plot for healthy participants in the MAD study is shown in Figure 2B and Table 3 shows a summary of PK parameters. Astegolimab demonstrated a dose-proportional serum PK profile for C_{max} and area under concentration–time curve over the dosing interval tau (AUC_{tau}) in the evaluated dose range of 70–210 mg SC.

Table 4 and Table S7 show a summary of PK parameters in healthy participants in the Japanese SAD study. Astegolimab exhibited linear PK in the dose range of 70–560 mg. Figure S4 shows the concentration–time plot for astegolimab and a comparison of PK parameters (C_{max} and AUC_{last}) between Japanese and White participants receiving 210 mg SC astegolimab in the Japanese SAD study. The overall and weight-adjusted geometric mean ratios for C_{max} (90% CI) in Japanese/White participants

TABLE 1 | Baseline characteristics (safety analysis set).

	SAD				MAD		Japanese SAD		
	Astegolimab in HP ($n=48$)	**Astegolimab in pAA ($n=2$)**	**Placebo in HP ($n=16$)**	**Placebo in pAA ($n=4$)**	**Astegolimab in HP ($n=30$)**	**Placebo in HP ($n=10$)**	**Astegolimab in JP ($n=25$)**	**Astegolimab in WP ($n=6$)**	**Placebo ($n=10$)**
Age (years), mean (SD)	30.9 (7.4)	36.0 (9.9)	27.7 (5.8)	32.5 (4.9)	31.1 (7.3)	30.7 (6.9)	32.0 (6.5)	26.7 (3.5)	28.3 (5.1)
Male sex, *n* (%)	47 (97.9)	1 (50.0)	15 (93.8)	3 (75.0)	30 (100)	10 (100)	25 (100)	6 (100)	10 (100)
Ethnicity, *n* (%)									
Hispanic/Latino	9 (18.8)	0 (0)	8 (50.0)	1 (25.0)	26 (86.7)	8 (80.0)	0 (0)	3 (50.0)	0 (0)
Not Hispanic/Latino	39 (81.3)	2 (100)	8 (50.0)	3 (75.0)	4 (13.3)	2 (20.0)	25 (100)	3 (50.0)	10 (100)
Race, *n* (%)									
Asian	5 (10.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	25 (100)	0 (0)	8 (80.0)
Black or African American	22 (45.8)	0 (0)	5 (31.3)	1 (25.0)	9 (30.0)	0 (0)	0 (0)	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	2 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White	17 (35.4)	2 (100)	10 (62.5)	3 (75.0)	21 (70.0)	10 (100)	0 (0)	6 (100)	2 (20.0)
Other	1 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Multiple	1 (2.1)	0 (0)	1 (6.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Weight (kg), mean (SD)	80.9 (10.9)	88.1 (8.3)	80.1 (13.6)	71.9 (11.9)	80.7 (10.9)	79.0 (14.0)	63.9 (9.8)	75.3 (7.0)	70.0 (10.6)
BMI (kg/m^2), mean (SD)	26.0 (3.0)	28.9 (1.6)	25.6 (3.1)	24.5 (2.5)	26.4 (3.3)	25.4 (2.6)	21.8 (2.7)	24.6 (2.1)	23.9 (3.8)

Abbreviations: BMI, body mass index; HP, healthy participants; JP, Japanese participants; MAD, multiple-ascending dose; pAA, patients with mild atopic asthma; SAD, single-ascending dose; SD, standard deviation; WP, White participants.

TABLE 2 | Summary of healthy participants with TEAEs in the SAD and MAD studies (safety analysis set).

	SAD		MAD	
	Astegolimab ($n=48$)	**Placebo ($n=16$)**	**Astegolimab ($n=30$)**	**Placebo ($n=10$)**
Participants with fatal TEAEs	0 (0)	0 (0)	0 (0)	0 (0)
Participants with ≥1 serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)
Participants with ≥1 TEAE leading to discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
Participants with ≥1 TEAE	24 (50.0)	7 (43.8)	16 (53.3)	6 (60.0)
Participants with ≥1 infection and infestation AE	9 (18.8)	5 (31.3)	5 (16.7)	2 (20.0)
Most common TEAEs[a]				
Upper respiratory tract infection	6 (12.5)	2 (12.5)	5 (16.7)	1 (10.0)
Headache	2 (4.2)	1 (6.3)	1 (3.3)	1 (10.0)
Increased blood creatine phosphokinase	1 (2.1)	0 (0)	2 (6.7)	0 (0)
Cough	2 (4.2)	1 (6.3)	0 (0)	0 (0)
Gastroenteritis	0 (0)	2 (12.5)	1 (3.3)	0 (0)
Laceration	2 (4.2)	0 (0)	1 (3.3)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)	2 (20.0)
Rash	2 (4.2)	0 (0)	0 (0)	0 (0)

Note: Data are *n* (%).
Abbreviations: MAD, multiple-ascending dose; SAD, single-ascending dose; TEAE, treatment-emergent adverse event.
[a]Occurring in ≥2 participants in the total astegolimab or total placebo cohort for either study.

treated with astegolimab 210 mg SC were 1.42 (1.05, 1.91) and 1.18 (0.90, 1.55), respectively, while the ratios for AUC_{last} (90% CI) were 1.54 (1.05, 2.26) and 1.13 (0.90, 1.44) based on analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models. No PK differences were observed based on ethnicity between Japanese and White participants after adjusting for body weight.

3.4 | Immunogenicity

The ADA response to astegolimab in healthy participants is summarized in Table S8. No participant treated with placebo developed ADAs, and no trends in ADA formation were observed across dosing cohorts.

In the SAD study, postbaseline ADAs were detected in 5/35 (14.3%) healthy participants treated with astegolimab SC and 4/12 (33.3%) participants treated with astegolimab IV who had a negative result at baseline. Most ADAs were transient, except in two participants treated with 700 mg IV astegolimab. No participants developed neutralizing ADAs in this study. None of the patients with mild atopic asthma developed ADAs.

In the MAD study, postbaseline ADAs were detected in 5/24 (20.8%) healthy participants treated with astegolimab SC and 3/6 (50.0%) treated with astegolimab IV. ADAs were transient in three (12.5%) participants treated with SC astegolimab (70 mg Q4W, 210 mg Q4W, 210 mg Q2W; $n=1$ each). One participant receiving 210 mg SC Q4W astegolimab developed neutralizing ADAs, but they were detected at the participant's end-of-study visit and did not result in any clinical consequences.

In the Japanese SAD study, postbaseline ADAs were detected in 7/30 (23.3%) healthy participants treated with astegolimab, including five Japanese participants. Four of the seven participants had transient ADAs, and no participant developed neutralizing ADAs.

In line with the data previously reported for the 21-mg, 70-mg, and 420-mg cohorts in the SAD study [14], ADA status did not affect PK in any of the three studies and there was no indication of an effect of ADA positive status on the incidence of allergic reactions and injection-site reactions (data not shown). Among the participants who developed ADAs, none had injection-site reactions or allergic reactions.

3.5 | Soluble ST2 Levels and Target Engagement

Full profile data for sST2 are not available for all cohorts in the SAD study because sST2 concentrations were assayed from PK samples at prespecified time points (Table S1). Baseline

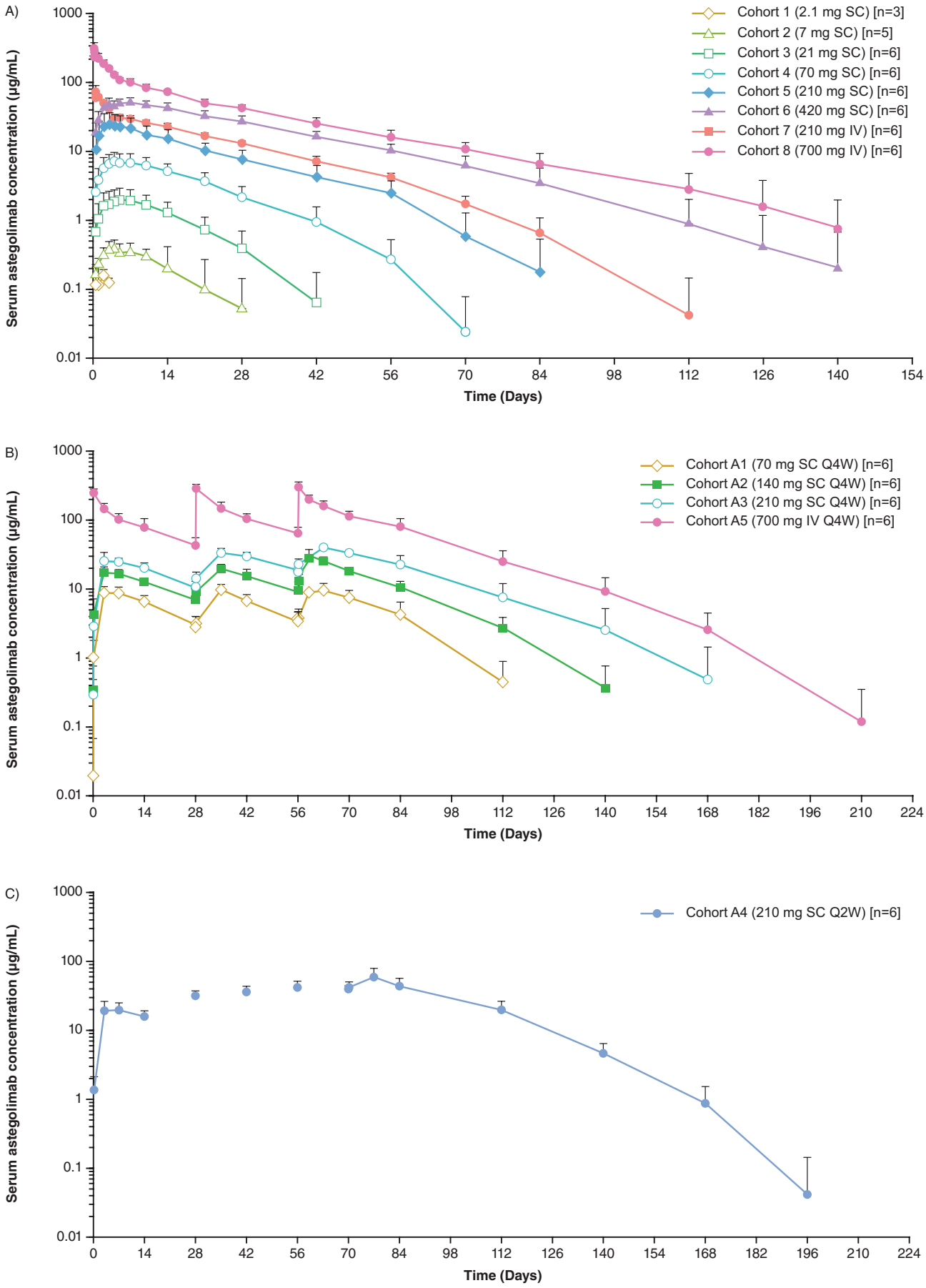

FIGURE 2 | Legend on next page.

FIGURE 2 | Mean (SD) serum astegolimab concentration–time curves for healthy participants in the (A) SAD study, (B) MAD study in the Q4W cohorts, and (C) MAD study in the Q2W cohorts[a] (PK analysis set). [a]Data are presented as time relative to the dose for the SAD study and time relative to the first dose for the MAD study. IV, intravenous; MAD, multiple-ascending dose; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks; SAD, single-ascending dose; SC, subcutaneous; SD, standard deviation.

TABLE 3 | PK parameters[a] for astegolimab in healthy participants in the SAD and MAD studies (PK parameter analysis set).

SAD	t_{max} (days)	C_{max} (μg/mL)	AUC_{last} (day×μg/mL)	$t_{1/2,z}$ (days)	AUC_{inf} (day×μg/mL)	CL[/F] (mL/day)	V_z[/F] (mL)
Subcutaneous dosing							
2.1 mg ($n=3$)	2.0 (0.50–2.0)	0.165 (0.0451)	0.367 (0.171)	NR	NR	NR	NR
7 mg ($n=5$)	3.0 (2.0–5.0)	0.401 (0.119)	4.38 (3.39)	10.3 (NR) [$n=1$]	12.6 (NR) [$n=1$]	557 (NR) [$n=1$]	8290 (NR) [$n=1$]
21 mg ($n=6$)[b]	6.5 (2.0–8.9)	2.10 (0.913)	35.6 (16.6)	7.41 (2.15) [$n=5$]	43.5 (12.3) [$n=5$]	519 (162) [$n=5$]	5360 (1510) [$n=5$]
70 mg ($n=6$)[b]	5.0 (3.0–8.9)	7.40 (2.60)	157 (57.3)	8.41 (2.29) [$n=5$]	180 (39.8) [$n=5$]	406 (89.1) [$n=5$]	4750 (812) [$n=5$]
210 mg ($n=6$)	3.0 (2.0–10.0)	25.6 (10.7)	582 (197)	12.0 (2.95)	597 (204)	384 (120)	6540 (2380)
420 mg ($n=6$)[b]	7.0 (6.0–7.1)	52.2 (9.25)	1870 (274)	11.8 (4.10)	1870 (279)	229 (35.4)	3850 (1160)
Intravenous dosing							
210 mg ($n=6$)	0.1 (0.1–0.1)	77.9 (7.8)	997 (62.3)	11.1 (1.69)	1000 (65.3)	210 (13.5)	3360 (544)
700 mg ($n=6$)	0.1 (0.1–0.1)	309 (29.9)	3730 (472)	18.7 (4.73)	3750 (504)	189 (24.6)	4990 (714)

	t_{max} (days)		C_{max} (μg/mL)		AUC_{tau} (day×μg/mL)		
MAD[c]	First	Last	First	Last	First	Last	AR[d]
Subcutaneous dosing							
70 mg Q4W ($n=6$)	3.0 (3.0–7.0)	4.0 (3.0–4.1) [$n=5$]	9.56 (1.59)	10.8 (3.31) [$n=5$]	169 (37.9) [$n=5$]	200 (61.5) [$n=5$]	1.20 (0.264) [$n=5$]
140 mg Q4W ($n=6$)	4.5 (2.9–7.1)	2.9 (1.9–3.1) [$n=5$]	17.6 (3.44)	28.6 (7.38) [$n=5$]	340 (51.8)	522 (86.4) [$n=5$]	1.47 (0.169) [$n=5$]
210 mg Q4W ($n=6$)	3.0 (2.9–14)	7.5 (1.9–8.0)	27.7 (4.98)	42.6 (3.44)	518 (78.2)	926 (76.9)	1.81 (0.218)
210 mg Q2W ($n=6$)	3.1 (3.0–8.1)	2.0 (0.0–7.0)	21.0 (6.44)	61.7 (20.2)	234 (65.0)	761 (234)	3.32 (0.782)
Intravenous dosing							
700 mg Q4W ($n=6$)	0.06 (0.06–0.17)	0.06 (0.06–0.17)	279 (44.2)	335 (57.1)	2560 (604)	3740 (667)	1.48 (0.151)

Abbreviations: AR, accumulation ratio; AUC_{inf}, area under the concentration–time curve from time 0 to infinity; AUC_{last}, area under concentration–time curve from time 0 to time of last quantifiable concentration; AUC_{tau}, area under concentration–time curve over the dosing interval tau (28 days post-dose for Q4W or 14 days post-dose for Q2W); CL, drug clearance after IV infusion; CL/F, apparent drug clearance after SC dosing; C_{max}, maximum observed drug concentration; IV, intravenous; MAD, multiple-ascending dose; NR, not reported; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; SAD, single-ascending dose; SC, subcutaneous; SD, standard deviation; $t_{1/2,z}$, terminal half-life; t_{max}, time to reach C_{max}; V_z, volume of distribution after IV infusion; V_z/F, apparent volume of distribution after SC dosing.
[a]t_{max} is reported as median (min–max); all other parameters are reported as mean (SD).
[b]Data for C_{max}, t_{max}, AUC_{last}, AUC_{inf}, and $t_{1/2,z}$ in the 21, 70, and 420 mg dosing cohorts in the SAD study have been previously published in Sperinde et al. [14].
[c]For MAD, parameters are presented for the first and last dose. Last dose is Day 57 for Q4W and Day 71 for Q2W.
[d]The AR is calculated as (AUC_{tau} after the last dose)/(AUC_{tau} after the first dose).

and postbaseline C_{max} sST2 concentrations are summarized in Table 5 and Table S9. sST2 change from baseline in healthy participants for the SAD and MAD studies is shown in Figure S5. Maximum sST2 concentrations generally increased as a function of astegolimab dose and dose frequency.

4 | Discussion

These Phase I studies in healthy participants and patients with mild atopic asthma demonstrate that astegolimab had an acceptable safety profile with no safety concerns identified. No

TABLE 4 | PK parameters[a] for astegolimab in healthy participants in the Japanese SAD study (PK parameter analysis set).

Cohort	t_{max} (days)	C_{max} (μg/mL)	AUC_{inf} (day × μg/mL)	$t_{1/2,z}$ (days)
70 mg SC, Japanese participants ($n = 6$)	4.1 (3.0–10)	12.1 (4.18)	336 (102)	9.14 (1.97)
210 mg SC, Japanese participants ($n = 6$)	6.0 (3.0–14)	30.5 (6.35)	1130 (409)	17.1 (4.59)
420 mg SC, Japanese participants ($n = 6$)	7.1 (6.0–10)	56.1 (15.3)	2080 (772)	14.8 (5.13)
560 mg SC, Japanese participants ($n = 6$)	5.0 (4.1–7.1)	78.4 (11.5)	2930 (497) [$n = 5$]	17.7 (3.97) [$n = 5$]
210 mg SC, White participants ($n = 6$)	7.0 (4.0–10)	22.1 (7.7)	721 (217)	11.6 (3.96)

Abbreviations: AUC_{inf}, area under the curve from time zero to infinity; C_{max}, maximum observed drug concentration; PK, pharmacokinetics; SAD, single-ascending dose; SC, subcutaneous; SD, standard deviation; $t_{1/2,z}$, terminal half-life; t_{max}, time to reach C_{max}.
[a]t_{max} is reported as median (min–max); all other parameters are reported as mean (SD).

serious or fatal AEs were reported, and no participants discontinued astegolimab due to an AE. Additionally, the type and incidence of AEs were similar in White and Japanese participants in the Japanese SAD study. The doses evaluated in these three studies were well tolerated, so the maximum tolerated dose of astegolimab was not identified. A Phase II study of astegolimab in patients with severe asthma (ZENYATTA) later evaluated astegolimab efficacy and safety at 70, 210, and 490 mg SC Q4W doses for 52 weeks and determined the highest dose also had an adequately tolerated safety profile with similar AE rates to the matching placebo [11].

In healthy participants in the SAD study, astegolimab exposure increased approximately dose proportionally in the dose range of 70–420 mg for single dosing but was greater than dose proportional in the overall range of 2.1–420 mg. This nonlinear PK profile at lower concentrations is characteristic of TMDD, where drug elimination is influenced by saturable binding to its target [15]. Indeed, when doses reached the linear range (≥ 70 mg), PK parameters such as clearance decreased, while $t_{1/2,z}$ increased, further reinforcing the involvement of TMDD. In turn, a significant fraction of astegolimab would be expected to be cleared via high-affinity, saturable target binding at lower doses, thus leading to faster apparent clearance and shorter $t_{1/2,z}$. When astegolimab dosing increases to the linear range, its primary clearance pathway shifts from this saturable, target-mediated clearance to linear, nonspecific clearance pathways, resulting in slower apparent clearance and longer $t_{1/2,z}$. This hypothesis is consistent with the results of a study that examined the nonlinear PK profile of astegolimab in the SAD study, where PK data were reanalyzed using the assay developed for the Phase II trials of astegolimab (which measured total astegolimab and was more tolerable to high target levels), revealing a 10-fold increase in astegolimab recovery with increasing sST2 concentrations compared with the Phase I assay, which measured only free astegolimab [14].

In the MAD study and Japanese SAD study, dose proportionality was demonstrated in the dose range of 70–210 and 70–560 mg, respectively. This suggests that the saturable binding sites were largely saturated within these dose ranges, allowing for linear elimination pathways to dominate. PK data from the Phase I studies informed the dosing of the ZENYATTA trial, which reported dose-proportional PK for 70–490 mg astegolimab Q4W [11]. Nonetheless, direct comparisons between observed PK in the Phase I and II studies cannot be made due to differences in PK assays.

In Japanese healthy participants, the increase in astegolimab exposure was also approximately dose proportional in the single-dose range of 70–560 mg, as evidenced by a 6.5- and 8.7-fold increase in C_{max} and area under the concentration–time curve from time 0 to infinity (AUC_{inf}), respectively, following an eight-fold increase in dose. Further analysis revealed that higher C_{max} values were observed in Japanese participants than in White participants, and body weight was found to contribute to the observed difference in astegolimab exposure, which was consistent with findings from a previous population PK analysis evaluating the effects of body weight on astegolimab PK [16].

Although the incidence of ADAs was ~14%–23% for SC administration and ~33%–50% for IV administration in the Phase I studies, subsequent Phase II studies of astegolimab have established a lower ADA incidence (2%–7%) [10–12]. These differences in ADA incidence could be the result of different patient populations and population sizes, as well as different ADA assay methods. The Phase I assay included an acid pretreatment step that could differentially impact high- and low-affinity ADAs, while the Phase II assay did not include that step to dissociate drug-bound ADA complexes [17]. However, the sensitivity of the Phase II assay was similar to the Phase I assay, and the drug tolerance of the Phase II assay was adequate to accurately detect ADAs based on the same surrogate positive control antibody that was utilized in the Phase I assay. Immunogenicity will continue to be assessed in future studies. In these three Phase I studies and the completed Phase II studies of astegolimab in patients with severe asthma or who were hospitalized with severe COVID-19 pneumonia, there was no correlation between ADAs and clinical findings or AEs [10, 11, 14].

The studies presented here examined sST2, a decoy receptor that binds free, bioactive IL-33. sST2 is formed via alternative splicing of the IL1RL1 gene (i.e., the gene that also encodes membrane-bound ST2) but the sST2 protein lacks the transmembrane and intracellular domains and is secreted into the extracellular space [1, 18, 19]. Both isoforms possess the same extracellular IgG domain, which is responsible for binding to the ligand IL-33 [19]. sST2 acts as a decoy receptor by sequestering active IL-33 to prevent binding to, and downstream activation of, the cellular ST2 receptor [1, 3]. In this way, sST2 can

TABLE 5 | Mean (SD) baseline sST2 and postbaseline C_{max} of sST2[a] by dosing cohort for healthy participants in the SAD and MAD studies (PK analysis set).

Dosing	Baseline sST2 (ng/mL)	sST2 C_{max} (ng/mL)[a]
SAD		
SC dosing		
Placebo	11.0 (4.5) [$n=12$]	12.6 (5.4) [$n=11$]
2.1 mg	12.9 (4.4) [$n=6$]	85.5 (25.1) [$n=5$][b]
7 mg	9.3 (4.7) [$n=6$]	106 (67.8) [$n=6$][b]
21 mg[c]	12.6 (4.7) [$n=6$]	198 (52.6) [$n=6$][b]
70 mg[c]	13.4 (4.6) [$n=6$]	266 (145) [$n=6$][b]
210 mg	12.8 (3.1) [$n=6$]	236 (67.1) [$n=6$][b]
420 mg[c]	10.6 (6.2) [$n=6$]	329 (164) [$n=6$]
IV dosing		
Placebo	16.2 (8.9) [$n=4$]	20.2 (9.9) [$n=4$]
210 mg	14.7 (5.0) [$n=6$]	82.0 (29.5) [$n=6$][d]
700 mg	9.6 (4.2) [$n=6$]	324 (148) [$n=6$]
MAD		
SC dosing		
Placebo	9.7 (3.4) [$n=8$]	68.0 (99.1) [$n=8$][e]
70 mg Q4W	9.3 (4.0) [$n=6$]	239 (78.4) [$n=6$]
140 mg Q4W	8.9 (3.8) [$n=6$]	298 (115) [$n=6$]
210 mg Q4W	9.0 (5.2) [$n=6$]	412 (212) [$n=6$]
210 mg Q2W	12.4 (5.0) [$n=6$]	475 (243) [$n=6$]
IV dosing		
Placebo	15.6 (NR) [$n=2$]	19.8 (NR) [$n=2$]
700 mg Q4W	21.9 (8.5) [$n=6$]	606 (160) [$n=6$]

Abbreviations: C_{max}, maximum observed concentration; IV, intravenous; MAD, multiple-ascending dose; NR, not reported; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; SAD, single-ascending dose; SC, subcutaneous; SD, standard deviation; sST2, soluble ST2; t_{max}, time to reach C_{max}.
[a]Refers to the highest observed sST2 concentration following the first dose (i.e., excluding baseline).
[b]C_{max} was calculated based on two post-baseline time points and may not reflect t_{max}: Day 8 and Day 113.
[c]Data for SAD 21-, 70-, and 420-mg doses have been previously published in Sperinde et al. [14]; data have been reanalyzed for the current publication.
[d]C_{max} was calculated based on two post-baseline time points and may not reflect t_{max}: Day 1 (2 h post-dose) and Day 113.
[e]Two recorded values of 209 and 246 ng/mL on Days 36 and 29, respectively, were ~4.3× and ~6.3× greater than the average at that time. If said values were excluded, the C_{max} (SD) would be 14.9 (7.5).

regulate or inhibit the biological effects of IL-33 and the subsequent inflammatory cascade [1, 3, 19]. The ability of sST2 to act as a negative regulator of IL-33 signaling [1, 19], combined with increased serum levels of sST2 and IL-33 found in patients with COPD compared with healthy individuals [20, 21], suggests that sST2 may play an important role in sequestering bioactive IL-33 and thereby limit overt IL-33–driven inflammation in patients with inflammatory pulmonary disease.

Overall, sST2 mean levels at baseline were in the range of 9–16 and 9–22 ng/mL for the SAD and MAD studies, respectively. Maximum post-dose sST2 concentration increased as a function of astegolimab dose and dosing frequency, likely due to the formation of astegolimab-ST2 complexes. This results in an accumulation of sST2 in serum by extending the half-life of sST2 due to the half-life of IgG2 antibodies (~23 days), indicating the target engagement of astegolimab [22]. A similar phenomenon was observed with an increase in IL-33 concentration in the presence of the anti–IL-33 itepekimab, which was attributed to the formation of an IL-33–itepekimab complex [23]. Nonetheless, the mechanism responsible for total sST2 increase post-dose is not fully understood.

The potential of increased sST2 concentrations to result in decreased IL-33 binding was also considered, but there is no evidence to support this in these Phase I studies. In the Phase IIa COPD-ST2OP trial evaluating astegolimab versus placebo in patients with COPD, the exacerbation rate ratio numerically favored patients with higher baseline sST2 (> 19.1 ng/mL) over lower sST2 (≤ 19.1 ng/mL), but there was no statistically significant difference in the interaction-by-treatment and sST2 subgroup [9]. These data suggest that astegolimab dose adjustments for patients with higher baseline concentrations of sST2 do not appear to be necessary; however, further studies would be required to provide a definitive answer.

The limitations of this study must be considered. Almost all the participants in these studies were male and, due to the typically small sample size of Phase I studies, interpretation of certain endpoints may be limited because the study was not powered to determine statistically significant effects. However, the safety profile observed in this study was validated in subsequent Phase II trials with larger populations, which also included a representative proportion of female participants [9–12].

These Phase I studies demonstrate that astegolimab has an acceptable safety and an encouraging PK profile which justifies further assessment in targeted patient populations. Following completed Phase II trials [9–12], astegolimab is currently being investigated in patients with COPD who have a history of frequent exacerbations in the Phase IIb ALIENTO and Phase III ARNASA clinical trials; patients who complete either of these trials can also enter the Phase III ALNASA open-label extension study, which will evaluate the long-term safety of astegolimab.

Author Contributions

J.R.P. designed and performed the research; W.Z., D.C., A.F., L.B., M.A.G., A.A., X.Y., A.D., H.W., J.R.P., and D.M. analyzed the data. All authors wrote the manuscript.

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Conflicts of Interest

W.Z. and D.C. are employees of Genentech Inc., and stockholders of F. Hoffmann-La Roche Ltd. A.F., L.B., M.A.G., A.A., X.Y., A.D., and D.M. are employees of Genentech Inc. H.W. and J.R.P. are employees and stockholders of Amgen Inc.

Data Availability Statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/innovation/process/clinical-trials/data-sharing.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** cts70338-sup-0001-supinfo.docx.