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RESEARCH ARTICLE

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Pharmacokinetics and safety of CT-P39 via auto-injector are comparable to reference omalizumab via pre-filled syringe

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ABSTRACT

Aims: To demonstrate pharmacokinetic equivalence of CT-P39 administered via auto-injector (CT-P39 AI) and European Union–approved reference omalizumab via pre-filled syringe (EU-OMA PFS) in healthy Japanese adults.

Participants & Methods: This open-label, Phase 1 study randomized participants (1:1) to a single 150 mg/mL dose of CT-P39 AI or EU-OMA PFS. The primary endpoint was pharmacokinetic equivalence per area under the concentration–time curve from time zero to infinity (AUC_{0-inf}) and maximum serum concentration (C_{max}). Equivalence was concluded if the 90% confidence intervals (CIs) for the ratios of geometric least-squares means (gLSMs) were contained within the predefined 80–125% equivalence margin. Secondary endpoints comprised additional pharmacokinetics, pharmacodynamics, safety, and immunogenicity.

Results: Overall, 65 and 64 individuals were randomized to CT-P39 AI and EU-OMA PFS, respectively. Pharmacokinetic equivalence between CT-P39 AI and EU-OMA PFS was demonstrated for both AUC_{0-inf} (ratio of gLSMs [90% CI] 101.66 [95.31–108.45]) and C_{max} (93.91 [87.20–101.14]). Thirty-nine (60.0%; CT-P39 AI) and 32 (50.8%; EU-OMA PFS) participants experienced treatment-emergent adverse events (TEAEs) with no serious TEAEs. Secondary endpoints were comparable between groups.

Conclusions: CT-P39 AI was pharmacokinetically equivalent to EU-OMA PFS following a single dose in healthy Japanese individuals; pharmacodynamics, safety, and immunogenicity were comparable.

PLAIN LANGUAGE SUMMARY

What is this article about?

A biosimilar is a medicinal product that is a highly similar copy of an original ("reference") medicine. Biosimilars are typically less expensive, so their use over reference medicines may increase patient access to treatment.

CT-P39 is a biosimilar determined by the European Medicines Agency to be highly similar to reference omalizumab, and approved to treat the same conditions, including asthma, chronic rhinosinusitis with nasal polyps, and chronic spontaneous urticaria. CT-P39 is approved for injection by a pre-filled syringe (PFS) device. An auto-injector (AI) device, which may be easier for patients to self-inject, has also been developed. In this study, healthy Japanese adults were given a single dose of either CT-P39 administered via an AI or reference omalizumab administered via a PFS.

What were the results?

Pharmacokinetics (what the body does to the drug – i.e. drug absorption, distribution, metabolism, and excretion), pharmacodynamics (the effect of the drug on the body), safety (the occurrence of side effects), and immunogenicity (the occurrence of immune responses to the drug) were comparable between the two groups.

What do the results of the study mean?

Previous pharmacokinetic studies with CT-P39 were conducted predominantly in healthy White adults. The current study's findings support generalizing the conclusions about CT-P39 similarity to reference omalizumab, as well as demonstrating that the different injection device did not affect the delivery or safety of the medication.

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KEYWORDS

Auto-injector; biosimilar; CT-P39; immunogenicity; omalizumab; pharmacokinetic; safety; therapeutic anti-IgE

1. Introduction

Omalizumab is a humanized monoclonal anti-immunoglobulin E (IgE) antibody [1,2] approved for the treatment of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), chronic spontaneous urticaria (CSU), and, in the United States (US) only, IgE-mediated food allergy [1,3]. IgE plays

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Article highlights

Introduction
- Omalizumab is a humanized monoclonal anti-immunoglobulin E (IgE) antibody approved for treating various allergic diseases, including asthma, chronic rhinosinusitis with nasal polyps, and chronic spontaneous urticaria.
- The omalizumab biosimilar CT-P39 is approved for administration via pre-filled syringe (PFS) in a growing number of countries, potentially facilitating increased patient access to omalizumab.
- Reference omalizumab is approved for administration via both PFS and auto-injector (AI) and an AI has been developed for CT-P39.

Methods
- This randomized, open-label, Phase 1 study assessed the pharmacokinetic (PK) equivalence of CT-P39 administered via AI (CT-P39 AI) versus European Union – approved reference omalizumab administered via PFS (EU-OMA PFS), in terms of area under the concentration – time curve from time zero to infinity (AUC_{0-inf}) and maximum serum concentration (C_{max}). Additional PK parameters, pharmacodynamics (PD), safety, and immunogenicity were also assessed.

Results
- PK equivalence between CT-P39 AI and EU-OMA PFS was demonstrated for both AUC_{0-inf} and C_{max} since the 90% confidence intervals for the ratios of the geometric least-squares means were contained within the predefined 80–125% equivalence margin.
- PD profiles for free and total IgE were comparable after CT-P39 AI or EU-OMA PFS administration.
- A single 150 mg dose of CT-P39 AI was well tolerated by the healthy Japanese study participants, and the overall safety profile was similar to that of EU-OMA PFS.
- No participants had positive anti-drug antibody results after CT-P39 AI or EU-OMA PFS administration.

Discussion
- This study supports the comparability of CT-P39 AI and EU-OMA PFS in terms of PK, PD, safety, and immunogenicity after a single dose.

a critical role in the allergic response [2,4] and is known to be elevated in allergic diseases [5]. Selective binding of omalizumab to IgE reduces the amount of free IgE, which, in turn, downregulates the expression of its high-affinity receptor (FcεRI), thereby inhibiting the IgE-mediated allergic cascade [1,2].

CT-P39 (Omlyclo®; Celltrion, Inc., Incheon, Republic of Korea) was developed as an omalizumab biosimilar. The use of biosimilars such as CT-P39 can reduce treatment costs relative to originator products, such as reference omalizumab, potentially increasing patient access to biologic treatment [6]. CT-P39 has been approved by regulatory agencies in a growing number of countries, including the European Medicines Agency (EMA) [7–10]. These approvals are based on the similarity of CT-P39 with reference omalizumab in terms of structure and function and on evidence that there are no clinically meaningful differences between them in terms of efficacy, pharmacokinetics (PK), safety, and immunogenicity [11–15]. To date, CT-P39 is the only omalizumab biosimilar that has been approved by the EMA [16].

Reference omalizumab is approved for administration subcutaneously via pre-filled syringe (PFS) and auto-injector (AI) [1,3], whilst CT-P39 is currently approved for subcutaneous administration via PFS only [7–10]. An AI has been developed for CT-P39 and is expected to offer several advantages over PFS, including with regard to ease of use [17,18], reduced pain [17,19], and improved adherence [20].

Following the demonstration of PK equivalence of PFS-administered CT-P39 and European Union (EU)-approved reference omalizumab [12], the current study was to serve as a bridge between CT-P39 administered via AI and CT-P39 administered via PFS by comparing CT-P39 AI and reference omalizumab PFS. Additionally, this study was conducted to secure approval for CT-P39 in Japan by bridging the results of global clinical trials of CT-P39 [12,15] with the Japanese population, in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E5 guidance [21]. The primary objective of this Phase 1 study was to demonstrate PK equivalence of CT-P39 administered via AI (CT-P39 AI) and reference omalizumab administered via PFS in healthy Japanese adults. The secondary objectives were to assess additional PK, pharmacodynamic (PD), safety, and immunogenicity endpoints up to Day 127.

2. Methods

2.1. Study design and treatment

This was a randomized, open-label, two-arm, parallel-group, single-dose, Phase 1 trial conducted in healthy participants at four study centers in Japan (Supplementary Table S1). Project management, clinical and medical monitoring, and reporting were performed under contract with IDD and PrimeVigilance Japan K.K. in collaboration with Celltrion, Inc. (Republic of Korea). Potential participants were screened from Day −28 to Day −2, and eligible participants were admitted to study centers on Day −1 for baseline assessments and to confirm eligibility status. Study assessments continued until the end-of-study visit on Day 127.

On Day 1, eligible participants were randomized (1:1) to receive a single subcutaneous dose (150 mg/mL) of CT-P39 AI or European Union–approved reference omalizumab via PFS (EU-OMA PFS). The study drug was administered into the outer upper arm on the non-dominant side by site-qualified, trained clinical staff. The randomization schedule was generated by unblinded biostatisticians using an interactive web response system, which linked randomization numbers to treatment codes. Randomization was stratified by Day −1 body weight (<70 vs ≥70 kg), serum total IgE level at screening (<40 vs ≥ 40 IU/mL), and sex (male vs female [self-reported, corroborated by medical records]). Although this was an open-label study, PK and immunogenicity data handling was done in a blinded manner with respect to sample analysis, data review, and parameter calculation before database lock.

This study followed the International Council for Harmonisation Guideline for Good Clinical Practice [22], the Declaration of Helsinki [23], and all national, state, and local laws or regulations. The study was not registered because it was conducted according to Japanese guidelines, which do not require clinical trials evaluating the bioequivalence of drugs manufactured using genetic recombination technology to be registered [24,25]. Participants provided written informed consent before study enrollment. The original protocol, informed consent form, and other written information regarding the study were approved by institutional review boards before study initiation (Supplementary Table S1).

2.2. Participants

Full eligibility criteria are described in the Supplementary methods. Eligible individuals were Japanese adults (self-reported, corroborated by medical records) aged 18–65 years (inclusive) who were healthy (defined as having no relevant abnormalities identified after a detailed medical history, physical examination, and clinical laboratory tests) and weighed >40 and ≤90 kg, with a body mass index of 18–29.9 kg/m^2. Participants were required to have a total IgE level ≤100 IU/mL at screening. Key exclusion criteria were current allergic reaction (including asthma, urticaria, angioedema, or eczematous dermatitis); history of anaphylactic shock or hypersensitivity (including clinically relevant drug hypersensitivity); history of or current immune complex disease, hyper-IgE syndrome, autoimmune disease, or bronchopulmonary aspergillosis; any current or previous treatment with anti-IgE monoclonal antibodies, or any agent targeting IgE; current parasitic infection or colonization on stool evaluation for ova and parasites; and use of medications within 2 weeks prior to study drug administration (and during the study) that could affect the study outcome.

2.3. Study endpoints

The primary objective was PK equivalence of CT-P39 AI and EU-OMA PFS, assessed in terms of the following primary endpoints: area under the concentration–time curve from time zero to infinity (AUC_{0-inf}) and maximum serum concentration (C_{max}). Secondary endpoints included additional PK parameters: time to maximum serum concentration (T_{max}), terminal half-life ($t_{½}$), percentage of AUC_{0-inf} obtained by extrapolation ($\%AUC_{ext}$), terminal elimination rate constant (λ_z), apparent total body clearance (CL/F), apparent volume of distribution during the terminal phase (V_z/F), and area under the concentration–time curve from time zero to last quantifiable concentration (AUC_{0-last}). Secondary PD endpoints were evaluated for free IgE (comprising minimum serum concentration [C_{min}], time to minimum serum concentration [T_{min}], and maximum percentage decrease from baseline) and total IgE (comprising C_{max}, T_{max}, and maximum percentage increase from baseline). Safety and immunogenicity were also evaluated as secondary endpoints.

2.4. Study assessments

Participants were admitted to the study clinic on Day −1 and discharged on Day 4 after confirmation that there were no clinically significant findings on the Day 3 assessments (Supplementary Table S2). Subsequent assessments were conducted during outpatient visits. Blood samples for PK, free IgE, and immunogenicity assessments were analyzed at Syneos Health, Inc. (Princeton, NJ, USA); total IgE was analyzed at local laboratories. Serum omalizumab concentrations and serum free IgE levels were measured using validated electrochemiluminescence methods (Meso Scale Discovery, Meso Scale Diagnostics, Rockville, MD, USA). Total IgE (i.e., free and omalizumab-bound IgE) was measured using ImmunoCAP™ Total IgE (Thermo Fisher Scientific, Uppsala, Sweden). PK parameters were determined using serum omalizumab concentrations by non-compartmental methods, using Phoenix WinNonlin™ (version 8.3; Certara, Inc., PA, USA). Serum omalizumab concentrations below the lower limit of quantification (0.016 µg/mL) were treated as 0 at the beginning of a participant's profile when the participant's profile was first assessed (i.e., before the first incidence of a measurable concentration) and missing thereafter. Free IgE concentrations below the lower or above the upper limit of quantification were treated as such (2.58 IU/mL and 165.29 IU/mL, respectively). Total IgE values below the lower limit of quantification (5 IU/mL) were set to 0.

Safety was assessed and clinical laboratory tests performed throughout the study (Supplementary Table S2). Safety assessments included monitoring treatment-emergent adverse events (TEAEs; including treatment-emergent serious adverse events [TESAEs], treatment-emergent adverse events of special interest [TEAESIs], and adverse device effects [ADEs]), clinical laboratory testing conducted at local laboratories, and local injection-site pain. TEAESIs were type I and III allergic reactions, injection-site reactions (ISRs), and parasitic (helminth) infections. TEAEs were coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (version 26.0) and graded for intensity according to the Common Terminology Criteria for Adverse Events (version 5.0). Local site pain was assessed using the 100 mm visual analog scale (VAS) within 15 minutes after study drug administration.

Anti-drug antibodies (ADAs) were evaluated using a validated electrochemiluminescent assay (sensitivity: 1.946 ng/mL) that followed a three-tiered approach (screening, confirmatory, and titer). Confirmed ADA-positive samples underwent further testing for titer determination using a titer assay that serially dilutes samples. The neutralizing antibody (NAb) activity of ADA-positive samples was characterized using a validated electrochemiluminescent assay (sensitivity: 164.983 ng/mL).

2.5. Statistical analysis

Analysis sets are detailed in the Supplementary methods. Log-transformed primary endpoints (AUC_{0-inf} and C_{max}) were analyzed using the analysis of covariance model with treatment as a fixed effect and Day −1 body weight, total IgE concentration at screening, and sex as covariates. PK equivalence between CT-P39 AI and EU-OMA PFS was concluded if the 90% confidence intervals (CIs) for the ratios of geometric least-squares means (gLSMs) were contained within a predefined equivalence margin of 80–125%. A sample size of 114 participants (57 in each group) was required to provide 90% statistical power to demonstrate PK equivalence, assuming a 35% coefficient of variation and an expected ratio of 1.03. To account for an expected 10% dropout rate, 128 participants (64 in each group) needed to be enrolled. Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Participant disposition and baseline characteristics

The first participant was randomized on 24 August 2023, and the last participant visit was on 31 January 2024. Overall, 527 individuals were screened, and 129 individuals were randomized to receive CT-P39 AI ($n = 65$) or EU-OMA PFS ($n = 64$)

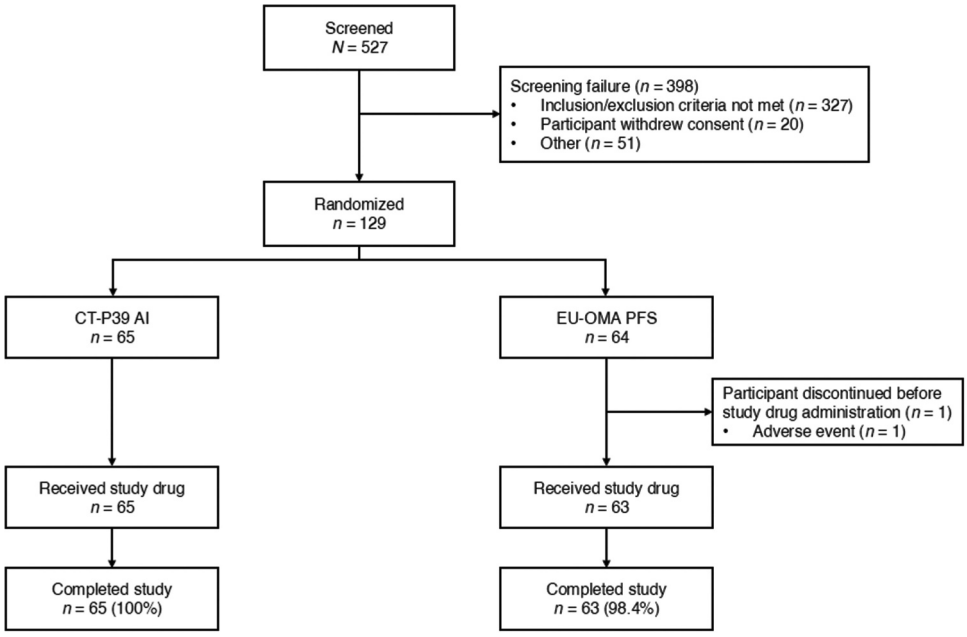

Figure 1. Participant disposition (ITT set).

AI: Auto-injector; EU-OMA: European Union–approved reference omalizumab; ITT: Intent-to-treat; PFS: Pre-filled syringe.

(Figure 1). One (1.6%) participant in the EU-OMA PFS group discontinued before study drug administration due to an adverse event (AE). All participants who received study drug completed the study. There were no major protocol deviations leading to exclusion from primary endpoint analysis.

Overall, participants were aged 18–63 years. Most participants were male ($n = 100$; 77.5%), and all were Asian. Demographics and baseline characteristics were similar between treatment groups (Table 1). The median (range) body weight at baseline was 61.30 (42.7–84.6) kg and 61.35 (42.0–87.3) kg in the CT-P39 AI and EU-OMA PFS groups, respectively; correspondingly, mean (standard deviation [SD]) total IgE concentration at screening was 44.32 (29.769) IU/mL and 44.73 (28.545) IU/mL.

3.2. PK

Mean (SD) serum concentrations of omalizumab were comparable between groups at each timepoint until Day 127 (Figure 2). PK equivalence between CT-P39 AI and EU-OMA PFS was demonstrated for both primary PK endpoints, AUC_{0-inf} and C_{max} (Table 2). The 90% CIs of the ratios for the gLSMs were contained within the

Table 1. Demographics and baseline characteristics for patients randomized to CT-P39 AI or EU-OMA PFS (ITT set).

	CT-P39 AI ($n = 65$)	EU-OMA PFS ($n = 64$)
Age (years), median (range)	40.0 (18–63)	38.0 (19–61)
Sex, n (%)		
Male	50 (76.9)	50 (78.1)
Female	15 (23.1)	14 (21.9)
Female fertility status, n (%)		
Postmenopausal	7 (46.7)	5 (35.7)
Potentially able to bear children	8 (53.3)	9 (64.3)
Race, n (%)[a]		
Asian	65 (100)	64 (100)
Ethnicity, n (%)		
Non-Hispanic or -Latino	65 (100)	64 (100)
Height (cm) at screening, median (range)	169.60 (145.7–181.2)	168.40 (148.4–182.3)
Weight (kg) on Day −1, median (range)	61.30 (42.7–84.6)	61.35 (42.0–87.3)
Weight (Day −1) category, n (%)		
<70 kg	54 (83.1)	50 (78.1)
≥70 kg	11 (16.9)	14 (21.9)
BMI (kg/m^2) at screening, median (range)	21.20 (18.2–28.2)	21.65 (18.2–29.9)
Serum total IgE level at screening (IU/mL), mean (SD)	44.32 (29.769)	44.73 (28.545)
Serum total IgE category at screening, n (%)		
<40 IU/mL	32 (49.2)	33 (51.6)
≥40 IU/mL	33 (50.8)	31 (48.4)

[a]Race was participant-reported.

AI: Auto-injector; BMI: Body mass index; EU-OMA: European Union–approved reference omalizumab; IgE: Immunoglobulin E; ITT: Intent-to-treat; PFS: Pre-filled syringe; SD: Standard deviation.

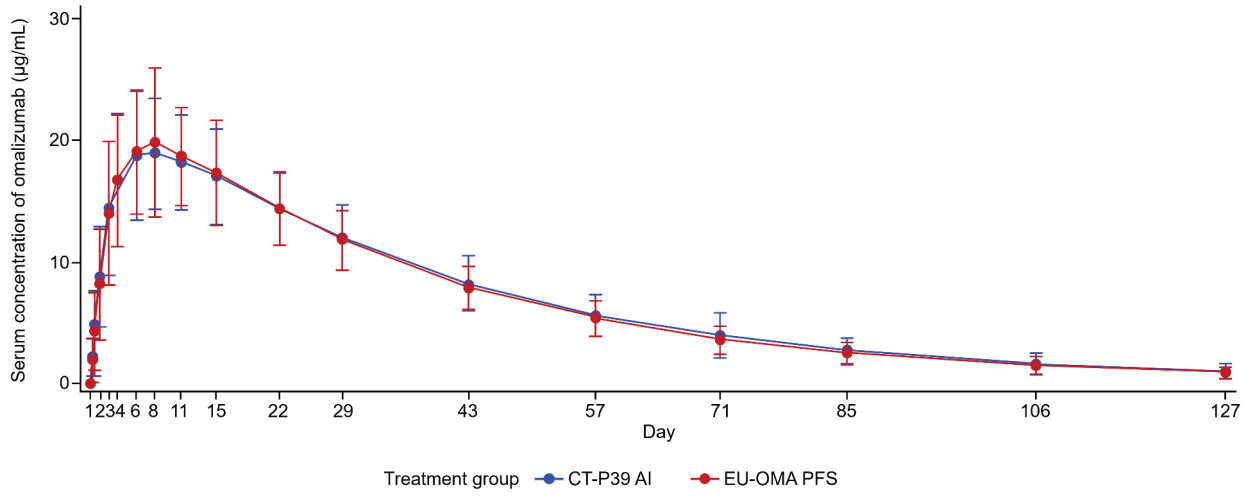

Figure 2. Mean (SD) serum concentration of omalizumab following a single dose on Day 1 of either CT-P39 AI or EU-OMA PFS (PK set).
AI: Auto-injector; EU-OMA: European Union–approved reference omalizumab; PFS: Pre-filled syringe; PK: Pharmacokinetic; SD: Standard deviation.

Table 2. Statistical analysis of the primary PK parameters of AUC_{0-inf} and C_{max} in the CT-P39 AI and EU-OMA PFS treatment groups (PK set).

Parameter (unit)	Treatment	n	gLSM	Ratio of gLSMs (90% CI)
AUC_{0-inf} (d·µg/mL)	CT-P39 AI	65	833.89	101.66
	EU-OMA PFS	63	820.24	(95.31–108.45)
C_{max} (µg/mL)	CT-P39 AI	65	18.41	93.91
	EU-OMA PFS	63	19.61	(87.20–101.14)

AI: Auto-injector; AUC_{0-inf}: Area under the concentration–time curve from time zero to infinity (extrapolated); CI: Confidence interval; C_{max}: Maximum serum concentration; EU-OMA: European Union–approved reference omalizumab; gLSM: Geometric least-squares mean; PFS: Pre-filled syringe; PK: Pharmacokinetic.

Table 3. Summary of mean (SD) primary and secondary PK parameters in the CT-P39 AI and EU-OMA PFS treatment groups (PK set).

Parameter (unit)	CT-P39 AI ($n = 65$)	EU-OMA PFS ($n = 63$)
AUC_{0-inf} (d·µg/mL)[a]	909.2 (230.10)	880.7 (197.64)
C_{max} (µg/mL)[a]	20.14 (5.1128)	21.46 (6.3159)
T_{max} (days)	6.664 (3.2140)	7.322 (3.2680)
$t_{½}$ (days)	27.93 (5.8771)	27.11 (7.2834)
$\%AUC_{ext}$ (%)	4.885 (2.8623)	4.379 (2.7380)
λ_z (1/day)	0.02577 (0.0047931)	0.02676 (0.0051629)
CL/F (L/day)	0.1767 (0.049885)	0.1825 (0.065235)
V_z/F (mL)	6884 (1525.1)	6930 (2125.6)
AUC_{0-last} (d·µg/mL)	860.6 (200.36)	839.9 (180.56)

[a]Primary PK endpoint.
λ_z: Terminal elimination rate constant; $\%AUC_{ext}$: Percentage of the area under the concentration–time curve from time zero to infinity, obtained by extrapolation; AI: Auto-injector; AUC_{0-inf}: Area under the concentration–time curve from time zero to infinity (extrapolated); AUC_{0-last}: Area under the concentration–time curve from time zero to the last measurable concentration; CL/F: Apparent clearance after subcutaneous dosing; C_{max}: Maximum serum concentration; EU-OMA: European Union–approved reference omalizumab; PFS: Pre-filled syringe; PK: Pharmacokinetic; SD: Standard deviation; $t_{½}$: Terminal half-life; T_{max}: Time to maximum concentration; V_z/F: Apparent volume of distribution during terminal phase.

80–125% equivalence margin. Additionally, secondary PK endpoints were comparable between groups (Table 3).

3.3. PD

Mean (SD) serum concentrations of free and total IgE were comparable between CT-P39 AI and EU-OMA PFS groups. Following study drug administration, free IgE concentrations rapidly decreased to a similar extent in each group, with the mean C_{min} in each group approaching the lower limit of quantification and recovered toward baseline afterward (Figure 3(a)). The elevation in total IgE after study drug administration and its return toward baseline were also comparable between groups (Figure 3(b)). PD parameters reflected the

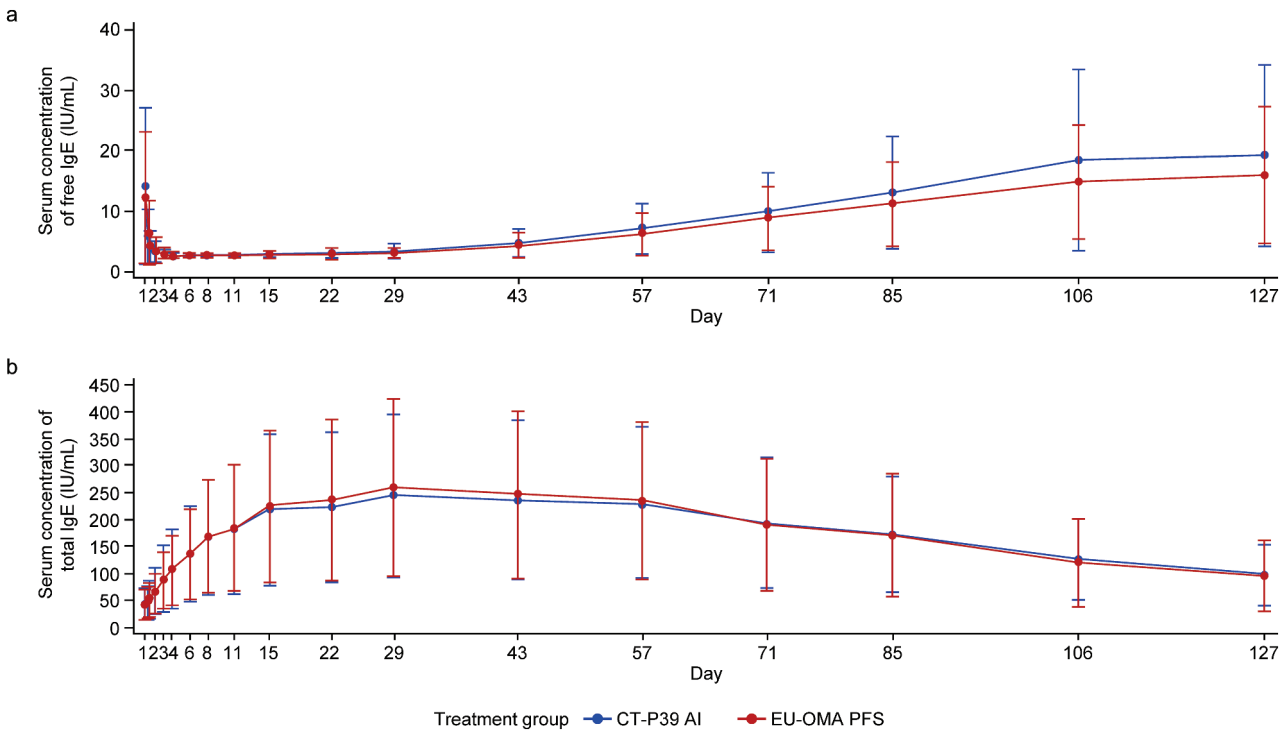

Figure 3. Mean (SD) serum concentrations of (a) free IgE and (b) total IgE following a single dose on Day 1 of either CT-P39 AI or EU-OMA PFS (PD set).
AI: Auto-injector; EU-OMA: European Union–approved reference omalizumab; IgE: Immunoglobulin E; PD: Pharmacodynamic; PFS: Pre-filled syringe; SD: Standard deviation.

comparability of free and total IgE response profiles between groups (Supplementary Table S3).

3.4. Safety

Overall, 126 TEAEs were reported in 71 participants (55.5%) (Table 4). The proportion of participants experiencing ≥1 TEAE was 60.0% ($n = 39$) and 50.8% ($n = 32$) in the CT-P39 AI and EU-OMA PFS groups, respectively. There were no deaths, TESAEs, TEAEs leading to study discontinuation, or TEAEs classified as ADEs.

The majority of TEAEs were Grade 1–2 in intensity. Two participants (1.6%) experienced Grade 3 TEAEs (CT-P39 AI: one participant [1.5%] with blood triglycerides increased; EU-OMA PFS: one participant [1.6%] with blood creatine phosphokinase increased). Both events resolved without treatment and the investigator considered them unrelated to the study drug. Nasopharyngitis was the most common any-grade TEAE in both groups (Supplementary Table S4).

In terms of TEAESIs, a similar number of participants in each group reported type III allergic reactions (CT-P39 AI: two [3.1%]; EU-OMA PFS: one [1.6%]) and ISRs (three [4.6%] and two [3.2%], respectively) (Table 4). The most frequently reported sign and symptom of ISR was injection-site erythema, reported in four participants (3.1%) (two [3.1%] and two [3.2%] in the CT-P39 AI and EU-OMA PFS groups, respectively) and injection-site pain, reported in one participant (1.5%) in the CT-P39 AI group. All TEAEs classified as ISRs were related to the study drug (i.e., CT-P39 AI and EU-OMA PFS) and were Grade 1–2 in intensity. All participants recovered from ISR events. No type I allergic reactions or parasitic (helminth) infections were reported.

Table 4. Summary of TEAEs in the CT-P39 AI and EU-OMA PFS treatment groups (safety set).

	CT-P39 AI ($n = 65$)	EU-OMA PFS ($n = 63$)
Total number of TEAEs	67	59
≥1 TEAE, n (%)	39 (60.0)	32 (50.8)
Study drug related	15 (23.1)	11 (17.5)
Classified as type III allergic reaction	2 (3.1)	1 (1.6)
Study drug related	2 (3.1)	1 (1.6)
Classified as ISR	3 (4.6)	2 (3.2)
Study drug related	3 (4.6)	2 (3.2)
≥1 TESAE, n (%)	0	0
TEAEs leading to death, n (%)	0	0
TEAEs leading to study discontinuation, n (%)	0	0
TEAEs classified as type I allergic reactions, parasitic (helminth) infections, or ADEs, n (%)	0	0

ADE: Adverse device effect; AI: Auto-injector; EU-OMA: European Union–approved reference omalizumab; ISR: Injection-site reaction; PFS: Pre-filled syringe; TEAE: Treatment-emergent adverse event; TESAE: Treatment-emergent serious adverse event.

The mean (SD) local site pain VAS scores were low and comparable between groups (9.7 [17.32] mm overall; 9.4 [17.80] mm and 10.0 [16.96] mm in the CT-P39 AI and EU-OMA PFS groups, respectively).

3.5. Immunogenicity

One participant (1.6%) in the EU-OMA PFS group had an ADA-positive result at baseline, prior to study drug administration, but had a negative NAb result. Following study drug administration, this participant was ADA negative; no AEs were reported in this participant. No participants had ADA-positive results after study drug administration.

4. Discussion

This study demonstrated PK equivalence between CT-P39 AI and EU-OMA PFS following administration of a single dose to healthy Japanese adults, assessed using the primary PK parameters AUC_{0-inf} and C_{max}. Secondary PK parameters, PD, safety, and immunogenicity outcomes were also similar between groups.

The PK equivalence (AUC_{0-inf} and C_{max}) of CT-P39 AI and EU-OMA PFS reported here is consistent with findings from the CT-P39 1.1 study (ClinicalTrials.gov, NCT04018313), which demonstrated the equivalence of AUC_{0-inf} and C_{max} between CT-P39, EU-OMA, and US-licensed reference omalizumab (US-OMA) administered via PFS in healthy adults [12]. Mean serum concentrations of omalizumab and PD parameters of free IgE and total IgE were generally comparable between CT-P39 AI and EU-OMA PFS in the current study, which is also consistent with previous studies demonstrating comparable PK and PD profiles between PFS-administered CT-P39 and reference omalizumab [12,15]. Population PK/PD analyses conducted for reference omalizumab have identified similar parameters across CSU, CRSwNP, and allergic asthma [26–28]. Taken together with results from the CT-P39 clinical development program, this suggests that the similarity in PK/PD profiles demonstrated between CT-P39 and reference omalizumab in healthy individuals and patients with CSU [12,15] is predictive of PK equivalence in CRSwNP and allergic asthma, as well as in CSU. Given the demonstration of equivalent efficacy between PFS-administered CT-P39 and EU-OMA in patients with CSU [15], we expect that comparable efficacy will be found between CT-P39 AI and reference omalizumab in the approved populations in real-world clinical practice.

In this study, a single dose of CT-P39 AI was well tolerated, and the overall safety profiles of CT-P39 AI and EU-OMA PFS were similar. This is aligned with previous comparisons of CT-P39 and reference omalizumab [12,15]. Other than two Grade 3 events considered unrelated to study drug, all TEAEs were Grade 1–2 in intensity. There was a slightly higher proportion of TEAEs reported in the CT-P39 AI group compared with the EU-OMA PFS group. Nasopharyngitis was the most common TEAE in both treatment groups, consistent with this being listed as a common event in the prescribing information for reference omalizumab [3]. TEAESIs of type III allergic reactions and ISRs were uncommon and there were no TEAESIs of type I allergic reaction or parasitic (helminth) infections. Overall, ISRs occurred in a numerically lower proportion of participants (4.6% [$n = 3$] CT-P39 AI; 3.2% [$n = 2$] EU-OMA PFS) than in the previous single-dose study comparing PFS-administered CT-P39 and reference omalizumab (17.0% [$n = 8$] CT-P39; 10.2% [$n = 5$] EU-OMA; 12.0% [$n = 6$] US-OMA) [12]. This suggests that the AI device was not associated with an increased incidence of ISRs compared with CT-P39 administered via PFS. No participants had an ADA-positive result after study drug administration in either group.

All participants in this study were Asian, possibly restricting generalizability; however, this study was conducted to secure approval for CT-P39 in Japan. Previous studies of reference omalizumab have reported comparable PK and PD findings across different races and ethnicities [29–32], and our findings are aligned with those of the CT-P39 1.1 study, which, despite having a predominantly White population, also showed no differences in outcomes based on race [12]. The comparable findings in both predominantly White and Japanese populations also support recent revisions to the regulatory guidance for assessment of biosimilars in Japan, which indicate that comparative clinical studies in a Japanese population are not necessary unless global studies have found an impact of ethnic factors on study results [33,34]. Although this study had to follow an open-label design due to visible differences in the drug administration devices, it is important to note that this would not be expected to impact the PK results as these data were analyzed in a blinded manner.

5. Conclusions

This study demonstrated equivalence of CT-P39 administered via AI and EU-OMA administered via PFS in terms of PK after a single dose in healthy Japanese individuals. PD, safety, and immunogenicity were also comparable between CT-P39 AI and reference omalizumab PFS.

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Author contributions

SHK, YB, SK, JEP, and JK contributed to the study design. TH, TE, MY, and RY contributed to data collection. All authors contributed to data analysis or interpretation, critically reviewed and critically revised the manuscript, approved the final version for publication, and agree to be accountable for the accuracy and integrity of the work.

Disclosure statement

CG reports ongoing consultancies with Blueprint Medicines, Celltrion, and Thermo Fisher Scientific; and has had previous consultancies with Argenx, Novartis, and Sanofi. SHK, YB, SK, JEP, and JK are all employees of Celltrion, with SHK, YB, and SK being Celltrion stock/shareowners. SS reports grant, research, and/or clinical trial support from Allakos, Amgen, Escient, Jasper, National Institutes of Health, Novartis, Regeneron, and Sanofi; and has served as a consultant or advisory board member for Allakos, Aquestive, Celltrion, Escient, Granular Therapeutics, Innate, Novartis, Regeneron, and Sanofi. The

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Ethical Declaration

This study was conducted in accordance with the International Council for Harmonisation Guideline for Good Clinical Practice [22], the Declaration of Helsinki [23], and all national, state, and local laws or regulations. The study was not registered because it was conducted according to Japanese guidelines, which do not require clinical trials evaluating the bioequivalence of drugs manufactured using genetic recombination technology to be registered [24,25]. Participants provided written informed consent before study enrollment. The original protocol, informed consent form, and other written information regarding the study were approved by the institutional review boards (Hakata Clinic Institutional Review Board, Fukuoka, Japan; Kitasato University Shirokane Campus Institutional Review Board, Tokyo, Japan; Osaka Clinical Trial Hospital Institutional Review Board, Osaka, Japan) before study initiation.

Data availability statement

The data that support the findings of this study are available in the article or uploaded as supplementary information.

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