



# Efficacy and Safety of Candidate Biosimilar CT-P43 Versus Originator Ustekinumab in Moderate to Severe Plaque Psoriasis: 28-Week Results of a Randomised, Active-Controlled, Double-Blind, Phase III Study

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## Abstract

**Background** CT-P43 is a candidate ustekinumab biosimilar in clinical development.

**Objectives** This paper aims to demonstrate equivalent efficacy of CT-P43 to originator ustekinumab in adults with moderate to severe plaque psoriasis.

**Methods** This double-blind, phase III trial randomised patients (1:1) to receive subcutaneous CT-P43 or originator ustekinumab (45/90 mg for patients with baseline body weight  $\leq 100$  kg/ $> 100$  kg) at week 0 and week 4 in Treatment Period I. Prior to week 16 dosing in Treatment Period II, patients receiving originator ustekinumab were re-randomised (1:1) to continue originator ustekinumab or switch to CT-P43; patients initially randomised to CT-P43 continued receiving CT-P43 (at weeks 16, 28 and 40). The primary endpoint of the trial was mean per cent improvement from baseline in Psoriasis Area Severity Index (PASI) score at week 12. Equivalence was concluded if confidence intervals (CIs) for the estimate of treatment difference were within pre-defined equivalence margins:  $\pm 10\%$  [90% CI; modified intent-to-treat set; Food and Drug Administration (FDA) approach] or  $\pm 15\%$  [95% CI; full analysis set for patients only receiving 45 mg doses in Treatment Period I; European Medicines Agency (EMA) approach]. Additional efficacy, pharmacokinetic, safety and immunogenicity endpoints were evaluated through week 52. Results to week 28 are reported here.

**Results** In Treatment Period I, 509 patients were randomised (CT-P43:  $N = 256$ ; originator ustekinumab:  $N = 253$ ). The mean per cent improvement in PASI score at week 12 was 77.93% and 75.89% for CT-P43 and originator ustekinumab, respectively (FDA approach); per the EMA approach, corresponding values were 78.26% and 77.33%. Estimated treatment differences were 2.05 (90% CI  $-0.23, 4.32$ ) and 0.94 (95% CI  $-2.29, 4.16$ ); equivalence was achieved for both sets of assumptions. Further efficacy parameters and pharmacokinetic, safety and immunogenicity outcomes were comparable between treatment groups, including after switching from originator ustekinumab to CT-P43.

**Conclusions** CT-P43 demonstrated equivalent efficacy to originator ustekinumab in patients with moderate to severe plaque psoriasis, with comparable pharmacokinetic, safety and immunogenicity profiles.

**Clinical Trial Registration** ClinicalTrials.gov Identifier: NCT04673786; date of registration: 17 December, 2020

## Key Points

This phase III trial was designed to compare a candidate ustekinumab biosimilar, CT-P43, to originator ustekinumab in adults with moderate to severe plaque psoriasis.

CT-P43 showed equivalent efficacy to originator ustekinumab, with comparable pharmacokinetics, safety and immunogenicity.

## 1 Introduction

Plaque psoriasis is a chronic, immune-mediated inflammatory disease, with an estimated prevalence of  $\geq 1.5\%$  in regions such as Australasia and Western and Central Europe, and in areas of North America [1]. Ustekinumab is a monoclonal antibody approved for the treatment of adults with moderate to severe plaque psoriasis, Crohn's disease, ulcerative colitis or active psoriatic arthritis (PsA) [2, 3]. It specifically targets the p40 subunit of the cytokines interleukin (IL)-12 and IL-23 and attenuates downstream cytokine signalling [3, 4], reducing expression of inflammatory

transcripts [3, 5]. Previous trials evaluating ustekinumab have consistently demonstrated a favourable safety profile [6–10].

The high cost of biologic therapies such as ustekinumab can be a barrier to patient access. Biosimilars, which have no clinically meaningful differences from the approved reference biologic, can help to address this challenge as lower-cost alternatives, encouraging more competitive pricing [11, 12]. Regulatory approval of biosimilars by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) is subject to demonstration of the absence of clinically meaningful differences in terms of safety, quality, biological activity and efficacy with respect to the originator biologic [11, 12]. There are currently no FDA- or EMA-approved ustekinumab biosimilars [13, 14].

CT-P43 is a candidate ustekinumab biosimilar currently in development. The safety and pharmacokinetics (PK) of CT-P43 have been investigated in a phase I study. We report week 28 findings from a phase III study comparing CT-P43 with originator ustekinumab in patients with moderate to severe plaque psoriasis. The primary objective was to determine equivalence of subcutaneously administered CT-P43 and originator ustekinumab in terms of efficacy at week 12, and to evaluate using two sets of equivalence margins ( $\pm 10\%$  and  $\pm 15\%$  to align with FDA and EMA approaches, respectively). Quality of life, PK, safety and immunogenicity were evaluated in addition to efficacy endpoints.

## 2 Methods

### 2.1 Study Design

This was a randomised, active-controlled, double-blind, phase III trial (ClinicalTrials.gov: NCT04673786) conducted at 34 centres in Estonia, Poland, Republic of Korea and Ukraine (Supplementary Table 1). Following initial screening from day 42 to day 1, patients were randomised (1:1) on day 1 to receive either CT-P43 or European Union-sourced originator ustekinumab in Treatment Period I (weeks 0–16; Fig. 1). Randomisation was conducted using an interactive web response system, which linked sequential patient randomisation numbers to treatment codes. At the first randomisation, patients were stratified by country, body weight ( $\leq 100$  kg versus  $> 100$  kg) and prior use of biologic treatment for psoriasis (yes versus no).

Following Treatment Period I, patients who had received originator ustekinumab were re-randomised (1:1) to either continue originator ustekinumab or switch to CT-P43 in Treatment Period II (weeks 16–40). The second randomisation was stratified by week 16 dose (45 mg versus 90 mg). Patients previously assigned to CT-P43 continued to receive

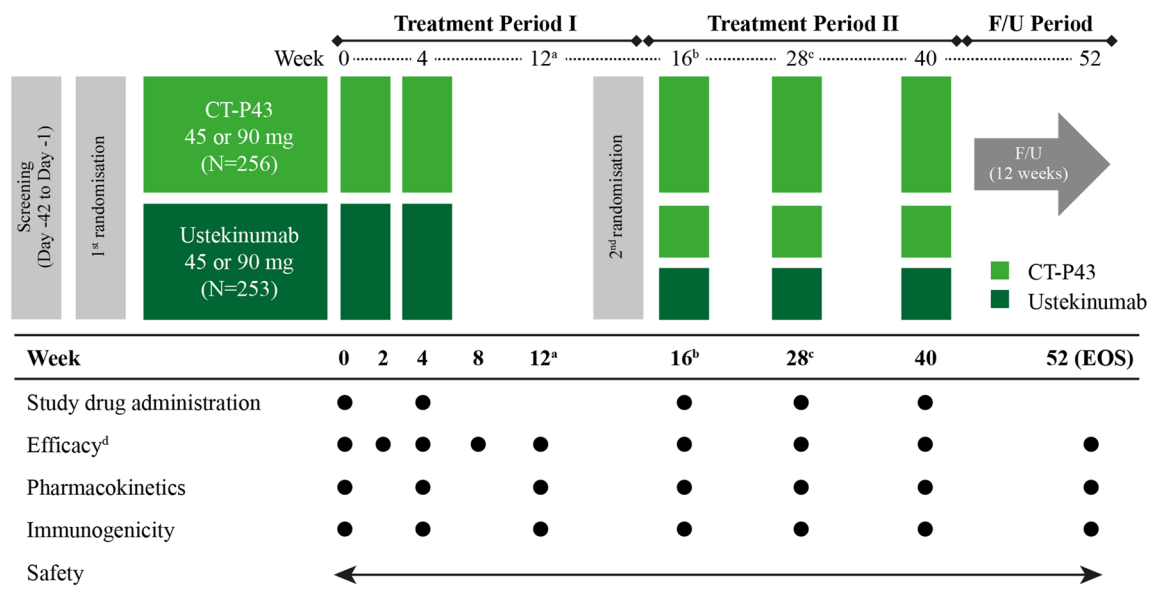
CT-P43. The study drug was administered at weeks 0 and 4 (Treatment Period I) and weeks 16, 28 and 40 (Treatment Period II) by subcutaneous injection via pre-filled syringe. During Treatment Period I, doses were 45 mg or 90 mg (two 45 mg/0.5 mL doses) for patients with baseline body weight  $\leq 100$  kg or  $> 100$  kg, respectively. Dosing for Treatment Period II was adjusted if a significant change in body weight had occurred pre-dose at week 16. There was a 12-week follow-up period after Treatment Period II and an end-of-study visit at week 52. This manuscript reports findings up to week 28.

Pre-defined personnel were unblinded for reporting purposes, following database lock for week 28 data. Other pre-defined personnel, investigators and patients remained blinded until end of study. Study drug administration was conducted by pre-defined unblinded staff at the site (as drug solutions had slightly different appearances).

The study was conducted according to Good Clinical Practice and the principles of the Declaration of Helsinki, as well as national, state and local laws or regulations. Study materials were approved by independent ethics committee/institutional review boards at each site (Supplementary Table 1). All patients in this manuscript have given written informed consent for participation in the study and the use of their de-identified, anonymized, aggregated data and their case details (including photographs) for publication. The original protocol was revised three times during the study period, including generation of two country-specific protocols (Supplementary Methods).

### 2.2 Patients

Full inclusion/exclusion criteria are included in the Supplementary Methods. Eligible patients were aged 18–80 years (inclusive), with plaque-type psoriasis diagnosed for  $\geq 24$  weeks prior to first study drug administration. Eligible patients had moderate to severe plaque-type psoriasis (defined as Psoriasis Area and Severity Index [PASI] score  $\geq 12$ , involved body surface area  $\geq 10\%$ , and static Physician's Global Assessment [sPGA] score  $\geq 3$ ), with or without PsA, at screening and first study drug administration, and were candidates for phototherapy or systemic therapy. Key exclusion criteria were diagnosis of other forms of psoriasis or skin conditions that could interfere with efficacy assessments, previous treatment with ustekinumab or candidate ustekinumab biosimilars and other drugs directly targeting IL-12 or IL-23, or  $\geq 2$  biologics approved for psoriasis treatment. Previous treatment with one biologic was allowed (with a sufficient washout period).



**Fig. 1** Study design. <sup>a</sup>At week 12, it was recommended that patients (in either group) who achieved at least PASI 50 continued study drug administration in Treatment Period II. <sup>b</sup>Prior to dosing at week 16, patients who were initially randomised to originator ustekinumab were re-randomised 1:1 to either continue receiving originator ustekinumab or to switch to CT-P43. <sup>c</sup>At week 28, it was recommended that only patients who achieved at least PASI 75 continued further study

drug administration (for all groups). <sup>d</sup>Investigator-reported outcome assessments were performed by a qualified efficacy assessor per site. It was recommended that the same assessor perform the investigator-reported outcome assessments throughout the entire study period, if possible. *EOS* end of study, *F/U* follow-up, *PASI 50/75* Psoriasis Area and Severity Index 50/75% improvement from baseline

### 2.3 Study Endpoints and Assessments

The primary efficacy endpoint was mean per cent improvement from baseline in PASI score at week 12. Secondary efficacy endpoints included: PASI scores, improvement from baseline PASI scores, proportions of patients achieving 50/75/90/100% improvement from baseline PASI scores (PASI 50/75/90/100), proportions of patients with sPGA scores of 0 (clear) or 1 (almost clear) and change from baseline in Dermatology Life Quality Index (DLQI) scores. PK, safety and immunogenicity were also assessed as secondary endpoints. Testing for anti-drug antibodies (ADAs) and neutralising antibodies (for patients with positive ADA results) against CT-P43 and originator ustekinumab was performed using an electrochemiluminescence assay (Meso Scale Discovery, Meso Scale Diagnostics, Rockville, MD, USA). PK assessment was based on serum drug concentrations at weeks 0, 4, 12, 16, 28, 40 and 52. Safety evaluations included treatment-emergent adverse events (TEAEs), coded according to the Medical Dictionary for Regulatory Activities version 24.1 and graded according to the Common Terminology Criteria for Adverse Events version 5.0. TEAEs of special interest were infections/serious infections, injection-site reactions (ISRs), hypersensitivity reactions and malignancies. Study assessments are summarised in Supplementary Table 2.

### 2.4 Statistical Analysis

Using FDA assumptions (described below), a minimum sample size of 400 patients was determined to provide  $\geq 90\%$  statistical power for demonstrating equivalence of the primary efficacy endpoint using a 90% confidence interval (CI) approach, corresponding to two one-sided tests at the 5% significance level. Calculations assumed an expected between-group difference of 0 and a standard deviation (SD) of 29.0 for the primary endpoint. Using EMA assumptions (described below), including only patients who received 45 mg doses of study drug during Treatment Period I, a minimum sample size of 166 patients was determined to provide  $\geq 80\%$  statistical power for demonstrating equivalence of the primary efficacy endpoint using a 95% CI approach, corresponding to two one-sided tests at the 2.5% significance level. Calculations assumed an expected between-group difference of 0 and an SD of 29.6 for the primary endpoint. A minimum sample size of 400 patients was estimated for the safety follow-up. With a hypothesised drop-out rate of 10%, a total sample size of 446 patients was planned.

The primary endpoint was analysed using analysis of covariance, as detailed in the Supplementary Methods. Covariates comprised country, body weight, use of prior biologic approved for psoriasis treatment and baseline PASI score. Using FDA assumptions, equivalence was concluded

if the 90% CIs for the treatment difference were entirely contained within the pre-defined -10% to 10% equivalence margin [using the modified intent-to-treat (mITT) set]. Using EMA assumptions, equivalence was concluded if the 95% CIs for treatment difference were entirely contained within the pre-defined -15% to 15% equivalence margin (in the full analysis set of patients who received only 45 mg doses of study drug in Treatment Period I, using complete case analysis). Analysis populations are detailed in the Supplementary Methods. Statistical analyses were conducted using Statistical Analysis System (SAS®) software (SAS Institute Inc., Cary, NC, USA) version 9.4.

## 3 Results

### 3.1 Patient Disposition

The first patient was randomised on 11 January 2021; the last patient's visit for week 28 occurred on 25 November 2021. Patient disposition is summarised in Fig. 2. In Treatment Period I, 509 patients were randomised (CT-P43:  $N = 256$ ; originator ustekinumab:  $N = 253$ ). There were three (1.2%) and four (1.6%) patients in the CT-P43 and originator ustekinumab groups, respectively, who discontinued the study. In Treatment Period II, 502 participants were re-randomised (253 continued CT-P43, 125 continued originator ustekinumab and 124 switched to CT-P43). Five patients discontinued the study or study drug during Treatment Period II up to week 28 (three in the continued CT-P43 group and two in the continued originator ustekinumab group).

Patient demographics were similar across groups (Table 1 for intent-to-treat [ITT] set; Supplementary Table 3 for ITT-Treatment Period II subset). Overall, 461 (90.6%) patients were White and 377 (74.1%) from Poland. Mean (SD) body mass index was 28.41 (5.60) kg/m<sup>2</sup>, 397 (78.0%) patients had baseline body weight  $\leq 100$  kg and mean (SD) involved body surface area was 25.2% (13.7). Mean (SD) time since plaque-type psoriasis diagnosis was 16.69 (11.899) years, 163 (32.0%) patients had concomitant PsA and 82 (16.1%) had received prior biologics approved for psoriasis treatment.

### 3.2 Efficacy

Equivalence was demonstrated between CT-P43 and originator ustekinumab for the primary efficacy endpoint of mean per cent improvement from baseline in PASI score at week 12 in both FDA and EMA analyses, as CIs for treatment differences were within pre-defined equivalence margins (Table 2). Results in the per-protocol set supported the primary analyses. 'Best-worst case' and 'worst-best case' sensitivity analyses for the primary endpoint were also supportive

(Supplementary Table 4). Absolute values and mean per cent improvement from baseline in PASI scores were generally similar between groups at all timepoints through week 28 (Fig. 3; Supplementary Tables 5, 6), as was the proportion of patients achieving PASI 50/75/90/100 (Supplementary Fig. 1; Supplementary Tables 7, 8).

The proportion of patients with an sPGA score of 0 or 1 was similar between treatment groups (Supplementary Fig. 2; Supplementary Tables 9, 10). The reduction in DLQI score from baseline was similar across treatment groups at weeks 12 and 28 (Table 3; Supplementary Tables 11, 12).

### 3.3 Pharmacokinetics

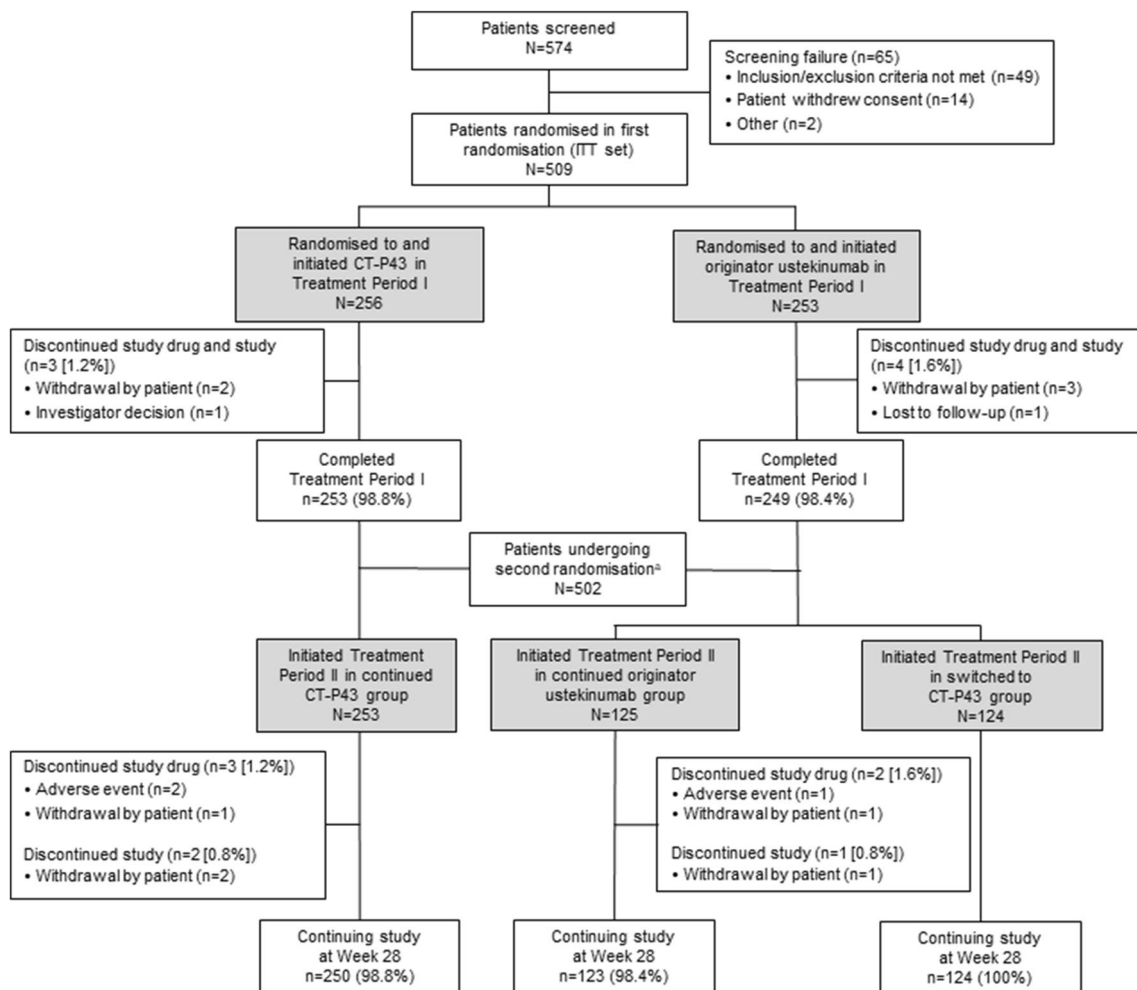
At all timepoints up to week 28, serum ustekinumab concentrations were generally similar between treatment groups and by dose (adjusted for baseline body weight), including after a single transition from originator ustekinumab to CT-P43 (Supplementary Tables 13, 14).

### 3.4 Safety

In Treatment Period I, 95 (37.1%) and 75 (29.6%) patients in the CT-P43 and originator ustekinumab groups, respectively, experienced at least one TEAE (Table 4). TEAEs related to study drug occurred in 18 (7.0%) and 15 (5.9%) patients in the CT-P43 and originator ustekinumab groups, respectively. Four (1.6%) patients in each group experienced treatment-emergent serious adverse events (TESAEs). One patient (in the CT-P43 group) experienced a TESAE of coronavirus disease 2019 (COVID-19) pneumonia that was considered possibly related to the study drug by the investigator. The TESAE was considered resolved 11 days after onset following appropriate treatment. Study drug was interrupted but later resumed. No TEAEs resulted in discontinuation of study drug.

In Treatment Period II (up to week 28), 40 (15.8%), 28 (22.4%) and 26 (21.0%) patients in the continued CT-P43 group, continued originator ustekinumab group and switched to CT-P43 group, respectively, experienced at least one TEAE (Table 5); correspondingly, four (1.6%), five (4.0%) and six (4.8%) patients experienced TEAEs related to study drug. There were no TESAEs during Treatment Period II. Two patients in the continued CT-P43 group and one patient in the continued originator ustekinumab group discontinued study drug owing to TEAEs related to hepatitis B [hepatitis B and hepatitis B surface antigen positive (0.8%), and hepatitis B DNA assay positive (0.8%), respectively]. No patients discontinued in the switched to CT-P43 group. There were no TEAEs resulting in death.

With regard to TEAEs of special interest, no TEAEs were classified as hypersensitivity reactions or malignancies



**Fig. 2** Patient disposition (ITT set). <sup>a</sup>The second randomisation process was carried out at week 16. Patients randomised to the CT-P43 group for Treatment Period I continued to receive CT-P43 in Treatment Period II. Patients assigned to originator ustekinumab for Treat-

ment Period I were randomised (1:1) to either continue originator ustekinumab or switch to CT-P43 in Treatment Period II. *ITT*, intent-to-treat

(Tables 4 and 5). TEAEs of infection occurred with similar frequencies across groups in both periods, with no serious infections during Treatment Period II. ISRs occurred at comparable frequencies across groups (Tables 4 and 5).

Overall, the majority of TEAEs were grade 1–2 in intensity; grade  $\geq 3$  TEAEs are detailed in Supplementary Table 15. The most frequent TEAEs are presented in Supplementary Table 16. There were no notable between-group differences in vital sign measurements or local injection-site pain. No active tuberculosis was reported.

### 3.5 Immunogenicity

In Treatment Period I, the proportion of patients with positive ADA results was generally lower in the CT-P43 group compared with the originator ustekinumab group (Supplementary Table 17). In Treatment Period II, there was no

overall change in ADA frequency following the single transition from originator ustekinumab to CT-P43 at week 16, compared with continuing originator ustekinumab. Pre-dose patients at week 28, 26 (10.3%), 21 (16.8%) and 22 (17.7%) in continued CT-P43, continued originator ustekinumab and switched to CT-P43 groups, respectively, were ADA positive. Overall, few patients (< 5%) without positive ADA results during Treatment Period I had positive ADA/neutralising antibody results in Treatment Period II.

Primary efficacy endpoint data were similar regardless of ADA positivity at week 12 and were also comparable between treatment groups within ADA-positive or ADA-negative subgroups (Supplementary Table 18). In Treatment Period I, serum ustekinumab concentrations were slightly lower in ADA-positive versus ADA-negative subgroups in both treatment groups (regardless of dose received); within subgroups, serum ustekinumab concentrations were

**Table 1** Baseline patient demographics, disease characteristics and stratification factors (ITT set)

	CT-P43 ( <i>N</i> = 256)	Originator ustekinumab ( <i>N</i> = 253)
Baseline patient demographics and disease characteristics		
Age (years), median (range)	41.0 (18–74)	41.0 (18–77)
Sex, <i>n</i> (%)		
Male	161 (62.9)	173 (68.4)
Female	95 (37.1)	80 (31.6)
Race, <i>n</i> (%)		
Asian	25 (9.8)	23 (9.1)
White	231 (90.2)	230 (90.9)
Ethnicity, <i>n</i> (%)		
Hispanic or Latino	1 (0.4)	1 (0.4)
Non-Hispanic or Non-Latino	255 (99.6)	252 (99.6)
Height (cm) at screening, median (range)	173.95 (151.7–213.0)	174.00 (141.0–195.0)
Body weight (kg), median (range)	84.25 (41.0–168.0)	86.00 (46.1–151.5)
Body mass index (kg/m <sup>2</sup> ), median (range)	27.515 (15.82–46.54)	27.920 (15.85–48.36)
Involved body surface area (%), mean (SD)	26.1 (14.2)	24.3 (13.2)
Time since plaque-type psoriasis diagnosis (years), mean (SD)	17.81 (12.144)	15.56 (11.560)
Concomitant PsA, <i>n</i> (%)	80 (31.3)	83 (32.8)
PASI score, mean (SD)	21.51 (7.939)	20.88 (7.998)
DLQI score, mean (SD)	13.2 (7.08)	11.9 (6.68)
sPGA score, mean (SD)	3.2 (0.37)	3.2 (0.38)
Prior use of non-biologic systemic agents, <i>n</i> (%)	155 (60.5)	146 (57.7)
Prior use of systemic steroids, <i>n</i> (%)	27 (10.5)	20 (7.9)
Stratification factors (first randomisation)		
Country, <i>n</i> (%)		
Estonia	5 (2.0)	6 (2.4)
Poland	189 (73.8)	188 (74.3)
Republic of Korea	25 (9.8)	23 (9.1)
Ukraine	37 (14.5)	36 (14.2)
Baseline body weight category, <i>n</i> (%)		
≤ 100 kg	198 (77.3)	199 (78.7)
> 100 kg	58 (22.7)	54 (21.3)
Use of prior biologic approved for psoriasis treatment, <i>n</i> (%)		
Yes	38 (14.8)	44 (17.4)
No	218 (85.2)	209 (82.6)

*DLQI* Dermatology Life Quality Index, *ITT* intent-to-treat, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis, *SD* standard deviation, *sPGA* Static Physicians Global Assessment

generally similar between treatment groups (Supplementary Table 19). In addition, there was no apparent correlation between ADA positivity and the occurrence of TEAEs, TESAEs, ISRs or hypersensitivity reactions during Treatment Period I (Supplementary Table 20).

## 4 Discussion

This study demonstrated equivalence of the candidate ustekinumab biosimilar CT-P43 to originator ustekinumab with respect to efficacy, as determined by mean

per cent improvement from baseline in PASI score at week 12. Equivalence was demonstrated using both FDA and EMA assumptions (in the mITT set and full analysis set of patients with a baseline body weight of ≤ 100 kg and therefore only receiving 45 mg doses of study drug in Treatment Period I, respectively). Secondary efficacy endpoints also demonstrated comparability between treatment groups, and findings remained comparable after patients receiving originator ustekinumab switched to CT-P43. PK and safety profiles were also comparable between CT-P43 and originator ustekinumab.

**Table 2** Improvement from baseline in PASI score at week 12 (mITT set, PP set and FAS)

Analysis protocol	Treatment group	<i>n</i>	LS mean (SE)	Estimate (CI) of treatment difference (%)
FDA <sup>a</sup>	mITT set			90% CI
	CT-P43	256	77.93 (1.771)	2.05 (−0.23, 4.32)
	Originator ustekinumab	253	75.89 (1.739)	
	PP set			90% CI
CT-P43	252	78.06 (1.767)	2.00 (−0.29, 4.29)	
Originator ustekinumab	244	76.06 (1.735)		
EMA <sup>b</sup>	FAS			95% CI
	CT-P43	198	78.26 (2.054)	0.94 (−2.29, 4.16)
	Originator ustekinumab	194	77.33 (2.049)	
	PP set			95% CI
	CT-P43	195	78.41 (2.038)	0.87 (−2.32, 4.07)
	Originator ustekinumab	193	77.54 (2.025)	

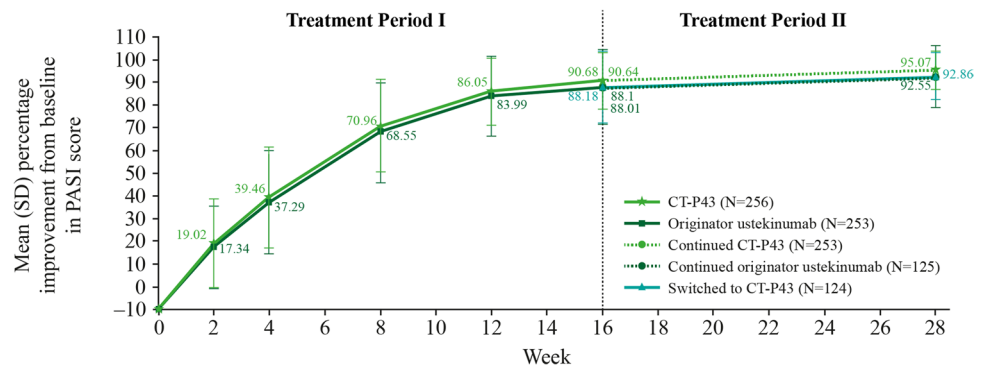
An ANCOVA was performed with the treatment as a fixed effect and country, baseline body weight, prior biologic use approved for psoriasis treatment and baseline PASI score as covariates

ANCOVA analysis of covariance, CI confidence interval, EMA European Medicines Agency, FAS full analysis set, FDA Food and Drug Administration, LS least squares, mITT modified intent-to-treat, PASI Psoriasis Area and Severity Index, PP per-protocol, SE standard error

<sup>a</sup>Analysis used ANCOVA and multiple imputation (per FDA protocol). In the case of the PP set, patients received study drug at weeks 0 and 4 and had PASI data available at baseline and week 12

<sup>b</sup>Analysis used ANCOVA (per EMA protocol). Patients who received ≥ 1 full 45 mg dose of study drug and did not receive any 90 mg doses in Treatment Period I were analysed. In the case of the PP set, patients received 45 mg doses of study drug at weeks 0 and 4 and had PASI data available at baseline and week 12

**Fig. 3** Percentage improvement from baseline in PASI score (mITT set). mITT modified intent-to-treat, PASI Psoriasis Area and Severity Index, SD standard deviation



**Table 3** Change from baseline in DLQI scores at weeks 12 and 28 (mITT set and FAS)

	Week 12		Week 28		
	CT-P43 (N = 256)	Originator ustekinumab (N = 253)	Continued CT-P43 (N = 253)	Continued originator ustekinumab (N = 125)	Switched to CT-P43 (N = 124)
Change from baseline in DLQI score					
<i>n</i>	255	248	250	124	124
Mean (SD)	−9.7 (6.74)	−8.5 (6.67)	−10.9 (7.20)	−8.8 (6.95)	−9.4 (6.66)
Median (range)	−9.0 (−28 to 7)	−7.0 (−29 to 7)	−10.0 (−27 to 14)	−8.0 (−28 to 8)	−8.5 (−29 to 2)

DLQI Dermatology Life Quality Index, FAS full analysis set, mITT modified intent-to-treat, SD standard deviation

**Table 4** Summary of TEAEs during Treatment Period I (safety set)

	CT-P43 ( <i>N</i> = 256)	Originator ustekinumab ( <i>N</i> = 253)
Total number of TEAEs	158	110
Patients with $\geq 1$ TEAE, <i>n</i> (%)	95 (37.1)	75 (29.6)
Related to study drug	18 (7.0)	15 (5.9)
Total number of TESAEs	4	4
Patients with $\geq 1$ TESAE, <i>n</i> (%)	4 (1.6)	4 (1.6)
Related to study drug	1 (0.4)	0
Total number of TEAEs leading to study drug discontinuation	0	0
Total number of TEAEs classified as infection	39	35
Patients with $\geq 1$ TEAE classified as infection, <i>n</i> (%)	34 (13.3)	32 (12.6)
Related to study drug	9 (3.5)	8 (3.2)
Total number of TEAEs classified as ISR	3	2
Patients with $\geq 1$ TEAE classified as ISR, <i>n</i> (%)	3 (1.2)	2 (0.8)
Related to study drug	3 (1.2)	2 (0.8)
Total number of TEAEs classified as hypersensitivity reaction	0	0
Total number of TEAEs classified as malignancy	0	0
Total number of TEAEs leading to death	0	0

ISR injection-site reaction, TEAE treatment-emergent adverse event, TESAE treatment-emergent serious adverse event

**Table 5** Summary of TEAEs during Treatment Period II (safety set – Treatment Period II subset)

	Continued CT-P43 ( <i>N</i> = 253)	Continued originator ustekinumab ( <i>N</i> = 125)	Switched to CT-P43 ( <i>N</i> = 124)
Total number of TEAEs	57	38	40
Patients with $\geq 1$ TEAE, <i>n</i> (%)	40 (15.8)	28 (22.4)	26 (21.0)
Related to study drug	4 (1.6)	5 (4.0)	6 (4.8)
Total number of TESAEs	0	0	0
Total number of TEAEs leading to study drug discontinuation	2	1	0
Patients with $\geq 1$ TEAE leading to study drug discontinuation, <i>n</i> (%)	2 (0.8)	1 (0.8)	0
Related to study drug	0	1 (0.8)	0
Total number of TEAEs classified as infection	14	7	8
Patients with $\geq 1$ TEAE classified as infection, <i>n</i> (%)	14 (5.5)	7 (5.6)	7 (5.6)
Related to study drug	1 (0.4)	3 (2.4)	1 (0.8)
Total number of TEAEs classified as ISR	1	0	2
Patients with $\geq 1$ TEAE classified as ISR, <i>n</i> (%)	1 (0.4)	0	2 (1.6)
Related to study drug	0	0	2 (1.6)
Total number of TEAEs classified as hypersensitivity reaction	0	0	0
Total number of TEAEs classified as malignancy	0	0	0
Total number of TEAEs leading to death	0	0	0

ISR injection-site reaction, TEAE treatment-emergent adverse event, TESAE treatment-emergent serious adverse event

The mean per cent improvement from baseline in PASI score at week 12 (primary endpoint) in both treatment groups was comparable with findings from the PHOENIX 1 and 2 studies [15, 16] and other phase II/III studies

of originator ustekinumab for the treatment of psoriasis [17–19]. Similarly, the proportions of patients achieving PASI 50/75/90/100 at weeks 12 and 28 were broadly



comparable with previous originator ustekinumab studies [15–19].

The safety profiles of CT-P43 and originator ustekinumab were similar in this study, including after switching from originator ustekinumab to CT-P43. Safety findings were consistent with the reported safety profile of originator ustekinumab [2]. Most TEAEs were grade 1–2 in intensity, and there were no hypersensitivity reactions, malignancies or deaths reported through 28 weeks. Unlike previous studies of ustekinumab, COVID-19 infection was one of the most frequently reported TEAEs, reflecting the period during which the study was conducted; however, the overall infection rate in this study was broadly comparable to previous reports [15–19]. Except for COVID-19 pneumonia, reported in two patients in the CT-P43 group and one in the originator ustekinumab group, the rate of TSEAEs was also similar to previous reports for originator ustekinumab [15–19].

The proportion of patients with positive ADA results was lower in the CT-P43 versus originator ustekinumab group in Treatment Period I, and similar trends were observed across groups in Treatment Period II. There was no change in ADA frequency after switching from originator ustekinumab to CT-P43. The impact of immunogenicity on clinical outcomes was similar between CT-P43 and originator ustekinumab during Treatment Period I; while positive ADA status was associated with reduced serum drug concentrations (in line with originator ustekinumab) [2, 3], there was no clinically significant impact of ADA status on efficacy or safety in terms of the occurrence of TEAEs, TSEAEs, ISRs or hypersensitivity reactions. Although the incidence of TEAEs was slightly higher in the CT-P43 versus originator ustekinumab treatment group (regardless of ADA positivity), this was not clinically significant.

The main strength of this study was the controlled study design and adequate statistical power to demonstrate equivalence of efficacy between CT-P43 and originator ustekinumab in patients with moderate to severe plaque psoriasis. One limitation was the absence of multiple switches in the study design, with only a single switch from originator ustekinumab to CT-P43 evaluated. Staff administering study drug could not be blinded to treatment assignment (due to marginal visual differences between the originator and biosimilar study drugs) but did not conduct other study assessments; patients and other investigators remained blinded. In addition, the study was conducted during the COVID-19 pandemic; while this did not result in any patients missing primary endpoint assessments, one and two patients in CT-P43 and originator ustekinumab groups, respectively, were excluded from the per-protocol set owing to protocol deviations arising from COVID-19. Data were collected on serum ustekinumab concentrations, although PK data had

also been collected previously [20]. This manuscript reports data up to week 28; final study results (up to week 52) will be published once available.

## 5 Conclusions

This study demonstrated the equivalence in terms of efficacy of CT-P43 and originator ustekinumab in patients with moderate to severe plaque psoriasis. The PK, safety and immunogenicity profiles of CT-P43 and originator ustekinumab were comparable. No notable safety issues or increase in immunogenicity were observed following a single switch from originator ustekinumab to CT-P43 group, compared with continued therapy with CT-P43 or originator ustekinumab.

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## Declarations

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**Data Availability** The data that support the findings of this study are available in the supplementary material of this article.

**Code Availability** Not applicable (no software or custom code).

**Ethics Approval** The study was conducted according to Good Clinical Practice and the principles of the Declaration of Helsinki, as well as national, state and local laws or regulations. Study materials were approved by independent ethics committee/institutional review boards at each site.

**Consent to Participate** All patients in this manuscript have given written informed consent for participation in the study and the use of their de-identified, anonymized, aggregated data and their case details (including photographs) for publication.

**Consent for Publication** Not applicable (no identifiable data).

**Author Contributions** KAP, MGL, DT, SK, YB, DJ, JJ, HL, TP, and WK contributed to the study design. JJ, BK, JT, AD, JCS, NR, JN, WB, JK, SD, KB-M, AR and YA collected study data. All authors contributed to data analysis or interpretation, reviewed and critically revised the manuscript, provided final approval of the version to be published, and agree to be accountable for accuracy and integrity.

**Congress Presentations** Selected data from the CT-P43 3.1 study were shared in an oral presentation at the 31st European Academy of Dermatology and Venereology (EADV) congress (7–10 September 2022; Milan, Italy).






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