London, 25 July 2013
EMA/CHMP/431551/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stelara

International non-proprietary name: USTEKINUMAB

Procedure No. EMEA/H/C/000958/II/0029

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ACCEPT	Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial
ACR	American College of Rheumatology
ADA	anti-drug antibody
ADR	adverse drug reaction
ACR	American College of Rheumatology
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASYM	asymmetric
AZA	azathioprine
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	body mass index
BQL	below the lowest quantifiable sample concentration of the assay (<LLOQ x MRD)
BSA	body surface area
BV	BioVeris™
CADMUS	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Ustekinumab in the Treatment of ADolescent Subjects with Moderate to Severe Plaque-type psoriasis
CCSI	Company Core Safety Information
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention
CERTIFI	Crohn's Evaluation of Response to Ustekinumab anti-IL12/23 for Induction
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organization of Medical Sciences
CLBA	competitive ligand binding assay
CL/F	apparent total systemic clearance of drug after extravascular administration
CMH	Cochran-Mantel-Haenszel
CRCL	creatinine clearance
CRF	case report form
CRP	C-reactive protein
CSR	Clinical Study Report
CV	cardiovascular
CV%	% coefficient of variance
DAS	Disease Activity Index Score
DAS28	disease activity index score 28
DBL	database lock
DBP	diastolic blood pressure
DIP	distal interphalangeal
DLQI	Dermatology Life Quality Index
DMARDs	disease-modifying antirheumatic drugs
ECLIA	electrochemiluminescent immunoassay
eCRF	electronic case report form
EE	early escape
EIA	enzyme immunoassay
EMA	European Medicines Agency
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FDA AERS	Food and Drug Administration Adverse Event Reporting System
HA	Health Authority

HAQ-DI	Disability Index of the Health Assessment Questionnaire
ICH	International Conference on Harmonisation
IFNγ	interferon gamma
IgG1κ	immunoglobulin G1 kappa
IJA	Independent joint assessor
IL	interleukin
IL-6	interleukin 6
IL-8	interleukin 8
IL-12	Interleukin-12
IL-23	Interleukin-23
ISS	Integrated Safety Summary
IV	intravenous
kg	kilogram
LFT	liver function test
LIV	liquid in vial
LLOQ	lower limit of quantification of the standard curve
LTE	long-term extension
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCP-1	macrophage chemoattractant protein 1
MCS	Mental Component Summary
MCSF-1	macrophage chemoattractant protein 1
MDC	macrophage derived chemokine
MedDRA	Medical Dictionary for Regulatory Activities
mg milligram	
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MPA	Swedish Medical Products Agency
MRD	minimum required dilution
MS	multiple sclerosis
MSD®	Meso Scale Discovery
MTX	methotrexate
NAb	neutralizing antibody
NK	natural killer
NIH	National Institutes of Health
NMSC	nonmelanoma skin cancer
NSAIDs	nonsteroidal anti-inflammatory drugs
pAb	Polyclonal Antibody
PASI	Psoriasis Area and Severity Index
PBC	primary biliary cirrhosis
PCS	physical component summary
PD	Pharmacodynamic(s)
PDCO	Paediatric Development Committee
PFS	prefilled syringe
PGA	Physician's Global Assessment (of disease severity)
PHOENIX	A Phase 3 multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque-type psoriasis followed by long-term extension
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
POLY	polyarticular
Ps	Plaque psoriasis
PsA	psoriatic arthritis
PsARC	Modified Psoriatic Arthritis Response Criteria
PSOLAR	PSOriasis Longitudinal Assessment and Registry

PSUMMIT	A Phase 3 Multicenter, Randomized, Double-blind, Placebo controlled trial of Ustekinumab, a Fully Human anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis
PSUR	Periodic Safety Update reports
PT	preferred term
PUVA	psoralen plus ultraviolet A light
q12w	every 12 weeks
RA	rheumatoid arthritis
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse events
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SEER	Surveillance, Epidemiology, and End Results
SD	standard deviation
SF-36	36-item Short Form Health Survey
SIR	standardized incidence ratio
SmPC	Summary of Product Characteristics
SOC	System organ class
SPON	spondyloarthropathy
t1/2	Half-life
TB	tuberculosis
Th	T helper
TNFα	tumour necrosis factor alpha
TRANSIT	An Exploratory TRial to Assess Naturalistic Safety and Efficacy Outcomes in Patients with Moderate to Severe Plaque Psoriasis Transitioned to Ustekinumab From Previous Methotrexate Therapy
UK	United Kingdom
ULN	upper limit of normal
US	United States
UVB	ultraviolet B light
VAS	Visual Analogue Scale (Score)
vdH-S	van der Heijde-Sharp
VEGF	vascular endothelial growth factor
V/F	apparent volume of distribution
WHO	World Health Organization
YKL-40	chitinase-3-like protein 1

1. Background information on the procedure

1.1. Type II

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 4 December 2012 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Stelara	USTEKINUMAB	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Addition of a new therapeutic indication - Psoriatic arthritis

“STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Stelara has been shown to improve physical function (see section 5.1).”

The MAH applied for a new indication for the treatment of psoriatic arthritis. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/292/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/292/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with

authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Derogation(s) of market exclusivity

Not applicable.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Ian Hudson** **Co-Rapporteur:** **David Lyons**

Submission date:	4 December 2012
Start of procedure:	21 December 2012
Rapporteur's preliminary assessment report circulated on:	11 February 2013
Co-Rapporteur's preliminary assessment report circulated on:	14 February 2013
Joint Rapporteur's updated assessment report circulated on:	15 March 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
MAH's responses submitted to the CHMP on:	22 May 2013
PRAC RMP advice and assessment overview adopted by PRAC	11 July 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	16 July 2013
CHMP opinion:	25 July 2013

2. Scientific discussion

2.1. Introduction

Therapies for PsA are intended to ameliorate disease signs and symptoms and the functional impairment caused by the disease, inhibit the structural damage resulting from inflammation, and improve quality of life in affected patients. Mild PsA can be effectively managed with nonsteroidal anti-inflammatory drugs (NSAIDs). DMARDs are the standard therapy for moderate to severe PsA. Methotrexate (MTX), cyclosporine, sulfasalazine, and leflunomide have been used in the treatment of this condition, and several anti-TNF agents have been approved for the treatment of PsA.

From a clinical perspective a clear need remains for alternative treatment options for patients with PsA who have inadequately responded to or are intolerant to NSAIDs, DMARDs and/or anti-TNF agents. There is room for new agents with a novel mechanism of action, which demonstrate consistent or improved efficacy across all components of PsA, improved safety, and a more convenient dosing schedule.

Ustekinumab (STELARA) is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds the p40 subunit common to the heterodimeric cytokines interleukin 12 (IL-12) and interleukin 23 (IL-23) and neutralizes their biological activities.

Ustekinumab has been authorised in the EU since 16 January 2009 and has received approval for the treatment of adult patients with chronic moderate to severe plaque psoriasis (Ps) in over 65 countries. This was primarily based on 2 large, Phase 3, placebo-controlled clinical studies (C0743T08 and C0743T09) in subjects with moderate to severe plaque psoriasis. In addition, ustekinumab has been studied or is currently being studied in multiple indications including psoriatic arthritis (PsA), paediatric psoriasis, Crohn's disease, multiple sclerosis (MS), primary biliary cirrhosis, sarcoidosis, and rheumatoid arthritis (RA).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

An overview of the 3 clinical studies that comprise the PsA clinical development program, including study populations, dose regimens, and efficacy endpoints is briefly presented in Table 1. Note that the older name for Stelara (ustekinumab) in the phase 2 Study C0743T10 is CNTO 1275.

Table 1: Overview of C0743T10, CNTO1275PSA3001 and CNTO1275PSA3002			
Design Elements	**C0743T10[a]**	**CNTO1275PSA3001[a]**	**CNTO1275PSA3002[a]**
Study Phase	2	3	3
Study Type	Proof of concept with induction dosing only	Induction and maintenance dosing	
Multicenter, Randomized, Placebo-controlled, Double-blind, Parallel Group	Yes	Yes	Yes
Study Population	Active PsA for at least 6 months with inadequate response to or intolerance to previous or current DMARDs and/or NSAIDs. Inclusion of up to 25% of subjects previously treated with anti-TNFα agents was allowed	Active PsA for at least 6 months with inadequate response to or intolerance to previous or current DMARDs and/or NSAIDs, but naïve to anti-TNFα agents	Active PsA for at least 6 months with inadequate response to or intolerance to previous or current DMARDs and/or NSAIDs. Inclusion of 50% to 60% of subjects previously treated with anti-TNFα agents was allowed
Duration of Efficacy Follow-up	36 weeks	100 weeks	52 weeks
Subjects enrolled	146	615	312
Treatment groups (n)	Placebo SC (n=70): Placebo SC at Weeks 0, 1, 2, 3 Placebo→90[b] mg SC at Weeks 12 and 16 90[b] mg SC (n=76): 90[b] mg SC at Weeks 0, 1, 2, and 3	Placebo SC (n=206): Placebo SC at Weeks 0, 4, 16, and 20 Placebo→45 mg SC at Weeks 24 and 28 followed by q12w dosing through Week 88 45 mg SC (n=205): 45 mg SC at Weeks 0 and 4 followed by q12w dosing through Week 88 90 mg SC (n=204): 90 mg SC at Weeks 0 and 4 followed by q12w dosing through Week 88	Placebo SC (n=104): Placebo SC at Weeks 0, 4, 16, and 20 45 mg SC at Weeks 24 and 28 followed by q12w dosing through Week 40 45 mg SC (n=103): 45 mg SC at Weeks 0 and 4 followed by q12w dosing through Week 40 90 mg SC (n=105): 90 mg SC at Weeks 0 and 4 followed by q12w dosing through Week 40
Primary Endpoint	ACR 20 response at Week 12	ACR 20 response at Week 24	ACR 20 response at Week 24
Major Secondary Endpoints in Order of Statistical Testing[b]	At Week 12 • ACR 50 response • ACR 70 response • Change from baseline in HAQ-DI • Change from baseline in DLQI • PASI 75 response	At Week 24 • Change from baseline in HAQ-DI • PASI 75 response • ACR 50 response • ACR 70 response • Change from baseline in total radio-graphic scores of the hands and feet[c]	At Week 24 • Change from baseline in HAQ-DI • PASI 75 response • ACR 50 response • Change from baseline in total radio-graphic scores of the hands and feet[c] • ACR 70 response

HAQ-DI = Health Assessment Questionnaire with Disability Index; DLQI = Dermatology Life Quality Index; ACR = American College of Rheumatology; PASI = Psoriasis Area and Severity Index; SC = subcutaneous; q12w = every 12 weeks; DMARD = disease modifying antirheumatic drug; NSAID = nonsteroidal anti-inflammatory drug; TNFα = tumor necrosis factor alpha

a. Additional details of study design are provided in Appendix A.1.
b. Order of statistical testing applies to Phase 3 studies only.
c. Pooled data from CNTO1275PSA3001 and CNTO1275PSA3002 (not included in this application).

2.3.2. Pharmacokinetics

A comprehensive PK analysis was provided at the initial MAA in subjects with plaque psoriasis. The additional data provided in this application is summarised below.

Assays

No updates were available for the assays used to detect serum ustekinumab concentrations.

There was a new validated assay developed for detection of antibodies to ustekinumab (Meso Scale Discovery ECLIA Method for Detection of Antibodies to Ustekinumab in Human Serum). The difference between this newer assay (ECLIA) and the older ADA assay provided in the initial MAA (EIA) is that

this newer assay incorporates an acid dissociation step and is therefore more tolerant to drug substance.

The older EIA and new ECLIA ADA methods were compared in a cross-validation that evaluated method sensitivity and ustekinumab interference in the ability of the methods to accurately detect antibodies to ustekinumab. The ECLIA method demonstrated greater sensitivity than the EIA method (1.97 ng/mL vs. 125 ng/mL respectively) when a purified cynomolgus anti-ustekinumab pAb was serially diluted.

Based on the screening Method A cut-point (0.132 OD), 50 ng/mL Cyno 6747 was detected in the presence of up to 7 ng/mL ustekinumab (CNTO 1275), whereas for the newer ECLIA the low positive ADA control (50 ng/mL Cyno 6747) could be detected in the presence of up to 100,000 ng/mL ustekinumab (CNTO 1275), thereby showing more tolerance to serum ustekinumab for the new ECLIA assay.

2.3.3. Pharmacodynamics

Mechanism of action

Efficacy for plaque psoriasis (Ps) was the main PD readout in the original MAA. In the Psoriatic Arthritis (PsA) studies the MAH conducted a variety of assessments for a PD effect other than clinical efficacy.

Assessments of serum markers previously reported to be associated with PsA were analysed. The serum inflammatory markers evaluated were VEGF, sIL-2R, MMP-3, and osteocalcin. Despite the reported association of elevated levels of these markers with PsA, in the study population the mean levels of all markers were not markedly elevated and were similar to those reported in the literature for healthy adults (Fink et al, 2007; Bons et al, 2007; Brennan et al 1997; Gundberg et al, 1983). Overall, there were minimal changes (< 10%) from baseline with no trend for change following treatment with ustekinumab.

2.3.4. PK/PD modelling

Population PK Analysis

A population PK analysis was performed examining a variety of demographics, baseline disease characteristics and concomitant medication.

There were 334 (48.0%) subjects who used concomitant MTX during the study period and were included in the population PK analysis. The median CL/F value in subjects who used concomitant MTX tended to be lower when compared with subjects who did not use concomitant MTX; the ratio of the median CL/F values in subjects who used concomitant MTX versus subjects who did not use concomitant MTX was 0.92 and the 90% CI of the ratio was (0.88, 0.96). Therefore, the use of concomitant MTX did not appear to affect the CL/F of ustekinumab in subjects with PsA.

Of the demographic factors (e.g., weight, gender, race, and age), baseline subject physical or biochemical characteristics, medical or medication history, or concomitant medications evaluated in the current population PK analysis, only subject weight and positive antibody to ustekinumab status were confirmed to be important covariates affecting the CL/F and therefore systemic exposure to ustekinumab in subjects with active PsA. However, the clinical relevance of the effects of these important covariates needs to be evaluated concurrently with the clinical efficacy and safety data. The PK simulation indicated that subjects of higher weight (>100 kg) had lower median serum ustekinumab concentrations compared with subjects of lower weight (≤100 kg), whereby the systemic

exposure to ustekinumab in subjects >100 kg treated with 90 mg doses was generally comparable to that in subjects ≤100 kg treated with the 45 mg doses. These findings are consistent with the results from the previous population PK analysis using data from Phase 3 plaque psoriasis studies. None of the other factors evaluated, such as concomitant medications (MTX, NSAIDs, or oral corticosteroids) and prior exposure to anti-TNF agents, appeared to have impacts on the CL/F of ustekinumab in subjects with PsA.

2.3.5. Discussion on clinical pharmacology

The MAH developed and validated an improved assay the ECLIA for detection of ADA. Serum samples were taken in all three trials described in this report. Data from the two pivotal trials were used for the population PK analysis.

The overall conclusions from these data are summarised below:

- In general, the PK and immunogenicity results from the PsA studies were consistent with those from the plaque psoriasis (Ps) studies submitted at the initial MAA.
- The median t1/2 of ustekinumab was estimated to be 22.4 days in the Phase 2 PsA study.
- Dose proportionality in serum ustekinumab concentration was observed in the PsA studies when comparing mean serum ustekinumab concentrations between the 45 mg and 90 mg groups.
- There was no evidence of accumulation in serum ustekinumab concentrations over time when ustekinumab was given SC q12w in the PsA studies.
- A higher proportion of subjects with BQL trough serum ustekinumab concentrations were observed in the 45 mg group compared with the 90 mg group in the PsA studies.
- Serum ustekinumab concentrations were affected by weight in subjects with PsA. Subjects >100 kg had lower mean serum ustekinumab concentrations compared with subjects ≤100 kg. Notably, mean serum ustekinumab concentrations in subjects >100 kg in the 90 mg group were generally comparable to those observed in subjects ≤100 kg in the 45 mg group.
- This was supported by population PK modeling and simulation.
- In the population PK analysis using Phase 3 PsA data, among the demographic factors (e.g., weight, gender, race, and age), baseline subject physical or biochemical characteristics, medical or medication history, or concomitant medications evaluated, only subject weight and positive antibody to ustekinumab status were found to be important covariates affecting the CL/F and therefore systemic exposure to ustekinumab in subjects with PsA.
    - In the population PK analysis, the use of concomitant MTX did not appear to have a clinically relevant impact on the CL/F of ustekinumab.
    - In the population PK analysis, prior exposure to biologic anti-TNF agents did not appear to have a clinically relevant impact on the CL/F of ustekinumab.
- Subjects with higher pre-injection serum ustekinumab concentrations tended to have higher clinical efficacy in PsA studies. The proportion of subjects who achieved ACR 20, ACR 50, and PASI 75 responses at Week 24 was higher in subjects with quantifiable preinjection serum ustekinumab concentrations at Week 16 when compared with subjects with preinjection BQL serum ustekinumab concentrations at Week 16.

- Population PK modeling showed that weight impacted systemic exposure to ustekinumab. Population PK/PD modeling showed a clear exposure-response relationship and that the impact of weight on efficacy resulted only from its impact on exposure to ustekinumab. This supports the concept of giving heavier subjects a higher dose of ustekinumab to achieve higher exposure to ustekinumab.
- The overall incidence of antibodies to ustekinumab was 5.8% to 6.1% through Week 24 in the Phase 3 PsA studies. The incidence of antibodies to ustekinumab was generally comparable between the 45 mg group and the 90 mg group in the PsA studies.
    - The incidence of antibodies to ustekinumab was lower in subjects receiving MTX at baseline (3.3% and 4.5%) compared with subjects not receiving MTX at baseline (8.1% and 7.6%) in the CNTO1275PSA3001 and CNTO1275PSA3002 studies, respectively.
    - The incidence of antibodies to ustekinumab was higher in subjects who were previously treated with biologic anti-TNF agents (8.5%) compared with subjects who were naïve to biologic anti-TNF agents (3.1%) in CNTO1275PSA3002.
- Subjects who were positive for antibodies to ustekinumab had lower mean serum ustekinumab concentrations than subjects who were negative for antibodies to ustekinumab in the PsA studies.
- Systemic markers of inflammation were measurable in the serum at baseline and 4 markers (MDC, VEGF, MCSF-1, and YKL-40) showed modest differences in concentration in ustekinumab-treated subjects compared to placebo at Week 4. However, there were no strong associations observed between the serum biomarkers measured and baseline disease severity or joint and/or skin response.

Patients with diabetes showed an apparent slightly increased clearance. The MAH performed a subgroup analyses for subjects with diabetes for the primary efficacy endpoint and the results showed that the PK and exposure in diabetic patients is within the 90% CI interval within the defined range (0.8-1.25) and that diabetes is not in itself a covariate that impacts on exposure from population PK analysis. The efficacy of patients with diabetes was also presented and although reduced compared with non-diabetic patients, no firm conclusions can be drawn in view of the small numbers with diabetes.

In Study C0743T10 use of a filter was introduced after the study commenced and had the effect of reducing the delivered dose of ustekinumab. The MAH clarified that the filter was introduced as a precaution following identification of particulate matter in other lyophilised products (not ustekinumab). Notably this lyophilised product used in study C0743T10 is not the marketed product. Although the dose administered was less (63 mg instead of 90mg as a result of loss of product in the filter), the PK data was as expected from the dose administered and there were no safety or efficacy concerns.

2.3.6. Conclusions on clinical pharmacology

The PK results were as expected and similar to the PK data from the initial MAA as the posology was the same in the 2 pivotal trials in PsA and the patient population are similar. The only difference between the PsA subjects and the Ps subjects was that in some PsA subjects there was concomitant MTX treatment. The MAH also provided extensive PD studies and separate report for these but there were no clear relationships with baseline disease or response to treatment.

Although the correlation of efficacy with serum levels of Stelara for outcome measures of PsA was not as clear as the correlation seen in the Ps programme at initial MAA (where much larger numbers of subjects were studied), throughout the PsA clinical trials efficacy was higher in the high dose groups. As exposure is less in those >100kg and a 90mg dose in those >100kg results in exposure similar to the 45mg dose in those <100kg, it is expected that those >100kg will benefit from the 90mg dose which is already licensed for Ps in those >100kg.

2.4. Clinical efficacy

2.4.1. Dose response study

Study C0743T10

Study C0743T10 was a Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of CNTO 1275 (CNTO 1275 was the name for ustekinumab at the time of study C0743T10), in Subjects with Active Psoriatic Arthritis (EudraCT No.: 2005-003525-92) 24 sites in the US, Canada, Finland, Denmark, and Switzerland Studied Period: 21 Dec 2005/20 Sep 2007

The Phase 2 study, C0743T10, was conducted to establish proof of concept for ustekinumab in PsA and to aid in determining the doses and dose regimens to be evaluated in Phase 3. Subjects enrolled in C0743T10 were required to have active PsA despite previous or current treatment with disease-modifying antirheumatic drugs (DMARDs) and/or non-steroidal anti-inflammatory drugs (NSAIDs).

Methods

This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, 2 arm study of CNTO 1275 90 mg in subjects with active PsA who had an inadequate response to current standard therapies (e.g., methotrexate [MTX], corticosteroids, NSAIDs, anti-tumour necrosis factor [anti-TNF] agents).

- **Study participants**

140 planned (70 subjects per group); 146 subjects were randomized to treatment and analysed for efficacy and for safety; 133 were analysed for pharmacokinetics and 124 were analysed for antibodies to CNTO 1275.

Men and women aged 18 years or older with active PsA (defined as disease for at least 6 months prior to study drug administration) who had an inadequate response to standard disease modifying antirheumatic drug (DMARD), and/or NSAID, and/or prior exposure to anti-TNF therapies.

DMARD therapy is defined as taking a DMARD for at least 3 months, or evidence of DMARD intolerance. Use of MTX at a dose ≤25 mg/week was allowed during the study but was not mandatory. Up to 25% of subjects may have had prior exposure to anti-TNF agents.

- **Treatments**

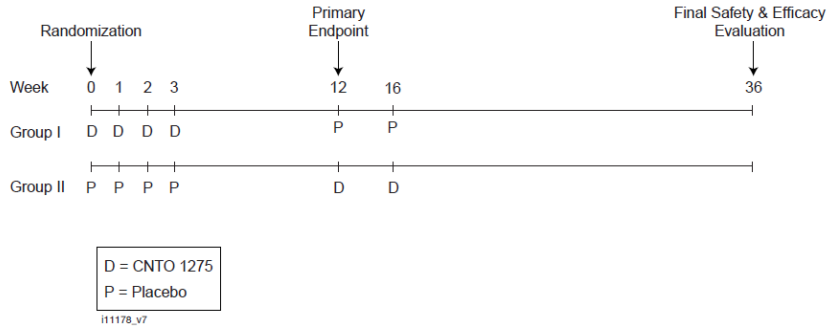
90 mg CNTO 1275 (or 63 mg after filtration) was administered by SC injection. Subjects randomized to CNTO 1275 x 4 were to receive CNTO 1275 at Weeks 0, 1, 2, and 3. At Week 12, subjects randomized to placebo were to receive CNTO 1275 63 mg at Weeks 12 and 16.

Placebo was administered by SC injection. Subjects randomized to placebo were to receive placebo injections Weeks 0, 1, 2, and 3. To maintain the blind, subjects randomized to CNTO 1275 x 4 were to receive placebo injections at Weeks 12 and 16.

The first to last administration of study agent was 16 weeks; pharmacokinetics, efficacy, safety, and antibodies to CNTO 1275 were evaluated through Week 36.

A schematic of the study design is provided in Figure 1. At Week 0, 146 subjects were randomized to SC injections of either ustekinumab 90 mg or placebo at Weeks 0, 1, 2, and 3. Placebo subjects crossed over to receive ustekinumab 90 mg SC at Week 12 and Week 16. After the first 36 subjects were enrolled in the study, the implementation of a filtration procedure during study dose preparation resulted in a dose volume reduction to approximately 0.70 mL, equivalent to approximately 63 mg for all subsequent doses. Fifty-nine of the 76 subjects who were randomized to ustekinumab and 57 subjects randomized to placebo were administered ustekinumab after the addition of the filtration step.

Figure 1: Study schema for Phase 2 PsA study C0743T10



- **Objectives**

The primary objective of this study was to evaluate the efficacy and safety of CNTO 1275 in the treatment of subjects with active psoriatic arthritis (PsA).

The secondary objectives were to evaluate:

(1) The efficacy of CNTO 1275 in achieving a high level of improvement in arthritis.

(2) The impact of CNTO 1275 on quality of life.

(3) The efficacy of CNTO 1275 on psoriatic skin lesions.

(4) The pharmacokinetic and pharmacodynamic characteristics of CNTO 1275 in subjects with PsA.

- **Outcomes / endpoints**

- Primary endpoint: the proportion of subjects with an American College of Rheumatology (ACR 20) response at Week 12;

- Major secondary endpoints:

  - proportion of subjects achieving an ACR 50 response at Week 12
  - proportion of subjects achieving an ACR 70 response at Week 12
  - change from baseline in the Disability Index of the Health Assessment Questionnaire (HAQ-DI) score at Week 12
  - for subjects with baseline ≥3% body surface area (BSA) psoriatic involvement, the change from baseline in Dermatology Life Quality Index (DLQI) score at Week 12

- for subjects with baseline ≥3% BSA psoriatic involvement, the proportion of subjects achieving a PASI 75 response at Week 12

Analyses of the primary and major secondary endpoints were stratified by subjects' prior anti-TNF exposure status.

Other efficacy assessments included assessments of dactylitis, enthesopathy, morning stiffness, Disease Activity Index (DAS) 28, and target lesions assessments. In addition, the relationship between serum CNTO 1275 concentration and efficacy was examined, as well as between antibodies to CNTO 1275 and efficacy.

Blood samples were collected from all subjects at each visit through Week 36 for the determination of serum CNTO 1275 concentration over time and t1/2. Antibodies to CNTO 1275 were determined from serum samples collected at Weeks 0, 12, and 36. Biomarkers were assessed at Weeks 0, 4, 12, and 36.

Statistical Methods

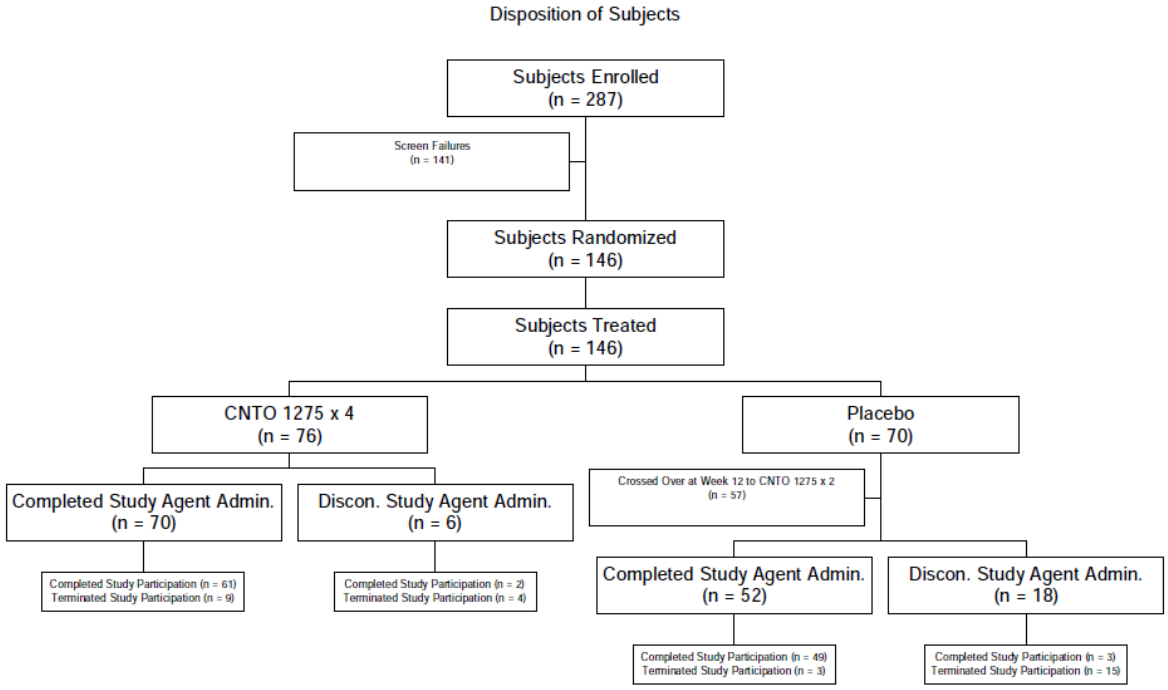
Simple descriptive statistics, such as mean, median, SD, interquartile range, minimum and maximum for continuous variables, and counts and percentages for categorical variables were used to summarize most data. Analyses were adjusted for subjects' status of anti-TNF exposure. All statistical procedures were performed 2-sided at a significance level of 0.05. The study was designed to maintain a Type I error of 0.05 or less for the primary analysis. Nominal p-values were to be reported for secondary analyses.

Results

- **Participant flow**

A total of 287 subjects were screened and 146 subjects were randomized, 76 subjects to CNTO 1275 and 70 subjects to placebo.

Figure 2 Subject disposition through Week 36 for subjects randomized at Week 0



Through Week 12, a higher percentage of subjects discontinued study agent in the placebo group (18.6%) compared with the CNTO 1275 x 4 group (5.3%).

The most common reasons for discontinuation of study agent in the placebo group were AEs and unsatisfactory therapeutic effect (4 [5.7%] each). No subjects in the CNTO 1275 x 4 group discontinued study agent for an AE of worsening PsA, psoriasis, or PsA and psoriasis. The most common reason for discontinuation in the CNTO 1275 x 4 group was unsatisfactory therapeutic effect for PsA only (2.6%).

- **Baseline data**

Baseline demographics and disease characteristics were generally comparable between the study groups. The majority of subjects were men (56.2%) and Caucasian (94.5%). The median age was 49.0 years, and the median weight was 90.91 kg. The median duration of PsA was 5.22 years while the median duration of Ps was 16.92 years. The total median numbers of swollen and tender joints at baseline were 9.0 and 18.0, respectively. The total median HAQ disability index was 0.8 and total median C-reactive protein (CRP) was 0.5 mg/dL. In subjects with ≥ 3% body surface area (BSA) involvement at baseline, the median PASI score was 8.70 and the median DLQI score was 10.5.

As the PsA population is at higher risk for comorbidity when compared with the general population and the study population had significant comorbidities in addition to PsA:

• past or current history of cigarette smoking was reported by 59.6% of subjects, with 29.5% still smoking at the start of study participation;

• hypertension was reported by 34.2% of subjects, with 30.1% requiring medication to control their hypertension;

• hyperlipidaemia was reported by 26.0% of subjects, with 17.1% requiring medication to control their hyperlipidaemia;

• depression was reported by 21.2% of subjects;

• diabetes mellitus was reported by 12.3% of subjects, with 2.7% requiring insulin to control their diabetes.

At baseline, 48.6% of subjects were using NSAIDs, 5.5% of subjects were taking COX-2 inhibitors, and 20.5% of subjects were using MTX. There were no subjects who were using oral corticosteroids.

- **Summary of results**

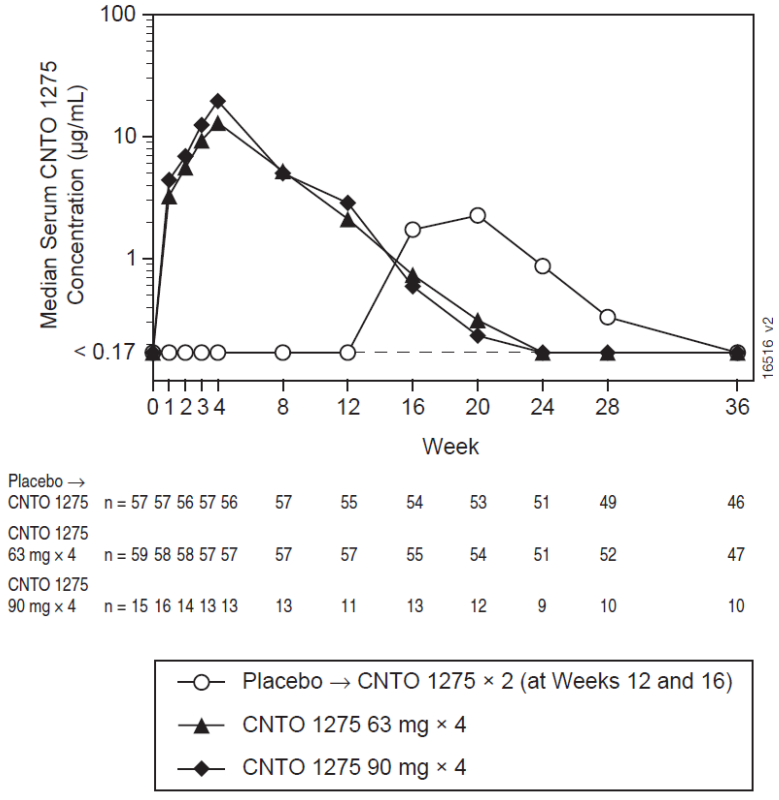
PK results

Of the 146 subjects with serum samples, 133 subjects received CNTO 1275 at least once during the study period and thus had evaluable serum CNTO 1275 concentrations. On days when study agent was administered, samples were taken immediately before the injection.

Serum CNTO 1275 Concentrations Over Time

After receiving 4 weekly doses of CNTO 1275 (at Weeks 0, 1, 2, and 3), the median serum CNTO 1275 concentrations generally peaked at Week 4 (the first available sampling time point after Week 3) and then declined exponentially through Week 20

Figure 3 Median serum CNTO 1275 concentrations (micrograms/mL) through Week 36; treated subjects



Median serum CNTO 1275 concentrations were below the LLOQ at Week 24 in subjects who received 63 mg x 4 and subjects who received 90 mg x 4. At each sampling time point from Week 1 through Week 4, serum CNTO 1275 concentrations were higher in subjects who received 90 mg x 4 than in subjects who received 63 mg x 4, with the difference between the 2 dosages showing an approximate dose-proportionality.

In the placebo → CNTO 1275 x 2 group, after receiving the second dose of CNTO 1275 at Week 16, median serum CNTO 1275 concentrations generally peaked at Week 20 (the first available sampling time point after Week 16) and then declined exponentially through Week 28. Median serum CNTO 1275 concentrations were below the LLOQ at Week 36.

Similar terminal elimination phases, in terms of the descending slopes of the median serum concentration versus time curves, were observed in the placebo → CNTO 1275 x 2 and CNTO 1275 x 4 groups regardless of dose.

Compared with subjects not receiving MTX at baseline, no consistent trends towards higher or lower serum CNTO 1275 levels were observed in subjects treated with MTX at baseline, suggesting that concomitant administration of MTX had no impact on the systemic exposure of CNTO 1275. However, interpretation is limited by the small number of subjects receiving MTX at baseline

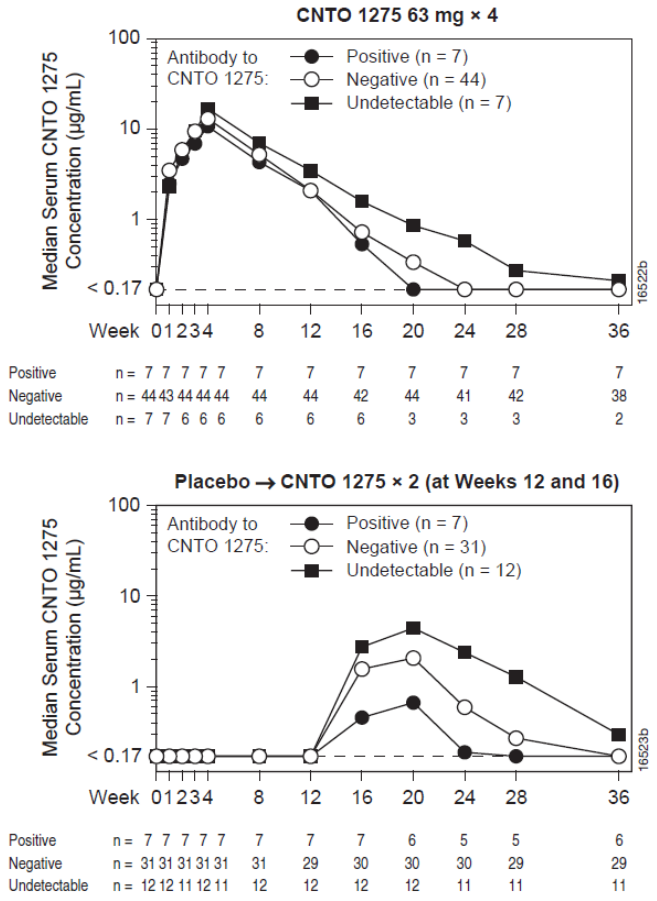
Serum CNTO 1275 Half-life

CNTO 1275 was eliminated from the circulation with a similar median t1/2 in subjects who received 63 mg x 4 and subjects who received 90 mg x 4. The overall median t1/2 of CNTO 1275 was 22.4 days.

Effect of ADA on PK

The number of subjects who were positive for antibodies to CNTO 1275 was low, and these subjects exhibited median serum levels of CNTO 1275 that trended lower than those in subjects either negative or undetectable for antibodies to CNTO 1275.

Figure 4 Median serum CNTO 1275 concentration over time by antibody to CNTO 1275 status and treatment groups; treated subjects



Although interpretation of the impact of immunogenicity on CNTO 1275 serum concentration is limited by the small study population and the small number of subjects positive for antibodies to CNTO 1275, there is a trend for lower serum levels in those who are ADA positive. This is similar to the results in the initial MAA for plaque psoriasis.

Pharmacodynamics

Assessments of serum markers previously reported to be associated with PsA were analysed (see section 2.3.3). Overall, there were minimal changes (< 10%) from baseline with no trend for change following treatment with CNTO 1275.

Efficacy results

Primary Endpoint

- ACR 20 Response at Week 12

The proportion of subjects who achieved the primary efficacy endpoint, ACR 20 response at Week 12, was significantly greater in the CNTO 1275 x 4 group compared with the placebo group (42.1% vs. 14.3%, $p < 0.001$.

A per protocol analysis including subjects who received all 4 correct injections within 2 weeks of the scheduled visit dates was performed. ACR 20 response at Week 12 was significantly greater in the CNTO 1275 x 4 group compared with the placebo group (45.7% vs. 16.9%, p < 0.001).

Major Secondary Endpoints:

- ACR 50 and ACR 70 Responses at Week 12

ACR 50 and ACR 70 responses at Week 12 were also compared. A significantly greater proportion of subjects in the CNTO 1275 x 4 group achieved an ACR 50 response and an ACR 70 response at Week 12 compared with the placebo group (25.0% vs. 7.1%, p = 0.004 and 10.5% vs. 0.0%, p = 0.005, respectively).

- Change From Baseline in the HAQ Score at Week 12

The functional status of subjects was assessed using the Disability Index of the HAQ. The improvement from baseline in the HAQ score is calculated such that negative values indicate improvement (i.e., less disability) and positive values indicate worsening (i.e., more disability). Reductions of ≥ 0.22 are considered clinically meaningful. The change from baseline in HAQ disability index at Week 12 was significantly greater in the CNTO 1275 X 4 group compared with the placebo group (median: –0.25 vs. 0.00, p < 0.001).

- Psoriasis Area and Severity Index Response at Week 12

In the subset of subjects with psoriasis involving ≥ 3% BSA at baseline, a significantly greater proportion of subjects in the CNTO 1275 x 4 group achieved a PASI 75 response compared with the placebo group (52.4% vs. 5.5%, p < 0.001).

- Change From Baseline in DLQI at Week 12

DLQI scores range from 0 to 30, with lower scores indicating better quality of life. A change from baseline is calculated such that negative values indicate improvement (i.e., better quality of life), and a decrease of 5 or more points from the baseline score (i.e., a change of –5) has been demonstrated to be clinically meaningful (Kimball et al, 2004).

At Week 12, among subjects with Ps involving ≥ 3% BSA at baseline, those in the CNTO 1275 x 4 group had a significantly greater decrease (improvement) in DLQI scores compared with those in the placebo group (median: 6.0 vs. 0.0, p < 0.001).

2.4.2. Main studies

Study CNTO1275PSA3001 (A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis.)

Methods

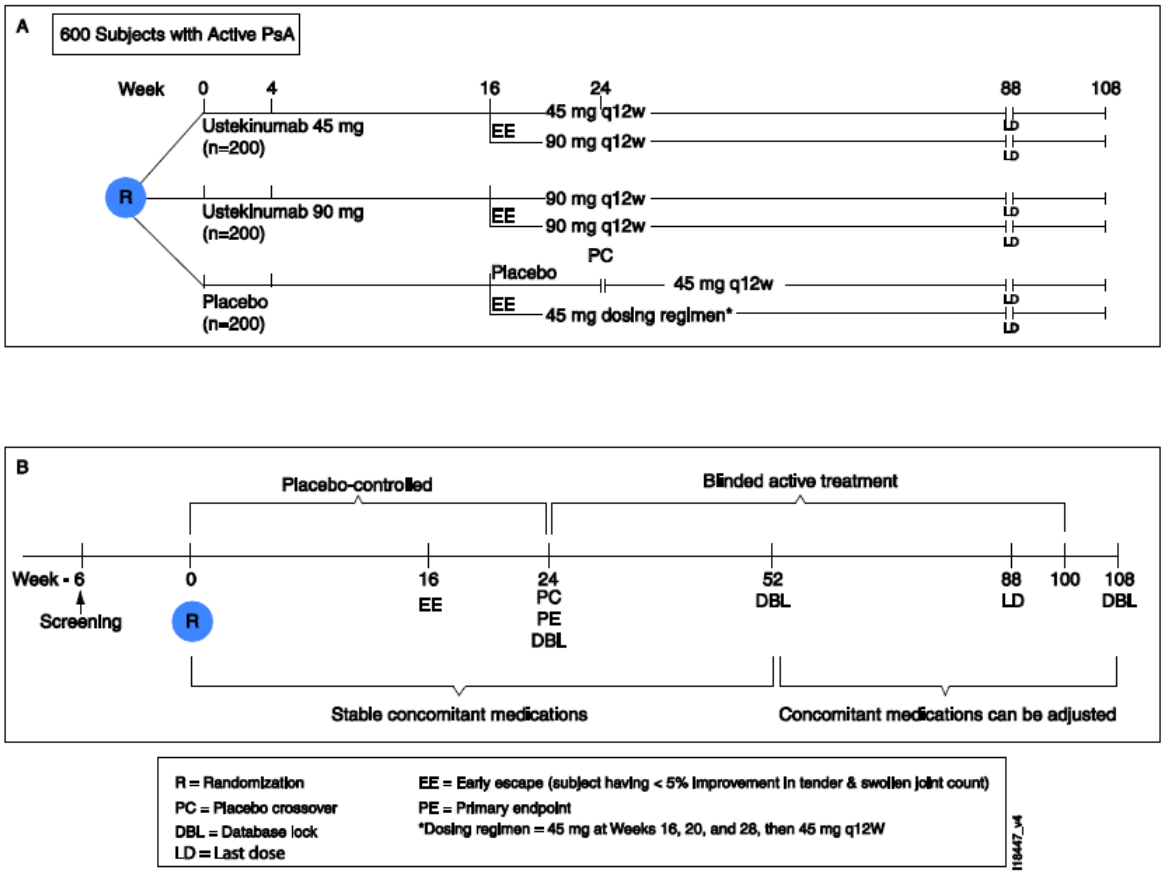
The CNTO1275PSA3001 (3001) study is an ongoing randomized, double-blind, placebo-controlled, parallel, multicenter 3-arm study (with early escape at Week 16) of ustekinumab in subjects with PsA. Approximately 600 subjects were planned to receive treatment with ustekinumab 45 mg, 90 mg, or placebo SC at Weeks 0 and 4 followed by q12w dosing with the last dose at Week 88. Subjects randomized to placebo were to crossover to receive ustekinumab at Weeks 24 and 28 followed by q12w dosing with the last dose at Week 88. Subjects will be followed for efficacy through Week 100 and for safety through Week 108.

All PK, efficacy, and safety data through Week 24 with the exception of the radiographic data for all randomized subjects were included in this DBL. In addition, subject disposition and safety data (including laboratory data) through Week 52 for subjects randomized prior to 26 Oct 2010 who were supposed to have completed Week 52 visit by the time of the 24-week DBL (either terminated the study or completed through Week 52), and referred thereafter as "the Week 52 safety subset", were also included. Radiographic data through Week 52 will be available in a subsequent DBL.

The expected duration of exposure to ustekinumab for randomized subjects is 100 weeks. Completion of the Week 108 visit will be considered the end of the study. Additional DBLs will occur at Week 52 and Week 108 with future reports planned to summarize the data through these time periods.

The Study Schema through Week 108 is presented in Figure 6

Figure 6: Schematic of Study CNTO1275PSA3001 through Week 108



Study participants

Subjects eligible for this study were men and women (excluding pregnant or nursing women, and men and women planning a pregnancy) aged 18 through 99 years who had a diagnosis of PsA for at least 6 months prior to first study agent administration and who had active PsA despite current or previous DMARD and/or NSAID therapy. Diagnosis of PsA must have included the diagnosis of active arthritis as defined by 5 or more swollen joints and 5 or more tender joints at screening and at baseline and high sensitivity CRP ≥0.3 mg/dL (decreased from ≥0.6 mg/dL per Amendment 3; upper limit of normal [ULN] 1.0 mg/dL) at screening, and the presence of active plaque psoriasis (Ps) or a documented history of Ps. As per study design, subjects were to be naïve with respect to anti-TNF therapy.

In addition, subjects must have had at least 1 of the following PsA subtypes: DIP joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis.

Subjects were eligible to participate if they had no evidence of active TB and no history of past latent TB. Subjects with latent TB newly detected at screening were eligible if they were started on treatment for latent TB prior to or simultaneously with first study agent administration. The study design excluded subjects with other inflammatory diseases that could confound the evaluations of benefit from ustekinumab therapy. Subjects who previously had been treated with anti-TNF therapy, received systemic immunosuppressives, or DMARDs other than methotrexate (MTX) within 4 weeks prior to the first study dose, were to be excluded from participation. Subjects who had received other specific drugs as outlined in the protocol were also excluded. Subjects who had used or were currently on a stable dose of MTX, NSAIDs, or oral corticosteroids were eligible for enrolment in the study. Subjects who had received topical or systemic Ps treatments as outlined in the protocol within the first 2 or 4 weeks of administration of study agent were excluded from participation in the study.

Treatments

Prior to the first injection, eligible subjects were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups as follows:

Ustekinumab 45 mg (n=205): Ustekinumab 45 mg at Weeks 0 and 4, followed by q12w dosing with the last dose at Week 88. At Weeks 20 and 24, subjects received placebo to maintain the blind.

Ustekinumab 90 mg (n=204): Ustekinumab 90 mg at Weeks 0 and 4, followed by q12w dosing with the last dose at Week 88. At Weeks 20 and 24, subjects received placebo to maintain the blind.

Placebo (n=206): Placebo at Weeks 0, 4, 16, and 20. At Weeks 24 and 28, subjects received ustekinumab 45 mg followed by q12w dosing with the last dose at Week 88.

At Week 16, subjects with <5% improvement from baseline in both tender and swollen joint counts were eligible to enter **early escape** in a double-blind fashion as follows:

Ustekinumab 45 mg: Ustekinumab 90 mg at Week 16, followed by 90 mg q12w dosing with the last dose at Week 88. At Weeks 20 and 24, subjects received placebo to maintain the blind.

Ustekinumab 90 mg: The same dosage schedule was to be continued.

Placebo: Ustekinumab 45 mg at Weeks 16, 20, and 28, followed by 45 mg q12w dosing with the last dose at Week 88. At Week 24, subjects received placebo to maintain the blind.

An additional dose was administered in the early escape arm because of operational reasons and the timing of placebo/active doses in the arms. The efficacy results from the early escape arm were descriptive only and not part of the formal comparisons between the treatment arms.

Objectives

The primary objectives of this study CNTO1275PSA3001 were to evaluate the efficacy of ustekinumab in subjects with active PsA by assessing the reduction in signs and symptoms of PsA and to evaluate the safety of ustekinumab in this population.

The secondary objectives of this study were to evaluate the efficacy of ustekinumab in:

- Improving physical function;
- Improving psoriatic skin lesions; and
- Inhibiting the progression of structural damage (this will be addressed in a future report).

The data on radiographic scores is not yet available. Regarding the efficacy of ustekinumab in reducing the rate of progression of structural damage in PsA, this will be established based on radiographic data collected from Phase 3 studies CNTO1275PSA3001 and CNTO1275PSA3002. A meta-analysis has recently been performed and a separate report is currently being prepared for inclusion in a variation submission, planned for later in 2013, in support of a STELARA PsA claim for structural damage.

Outcomes / endpoints

The primary endpoint was the proportion of subjects achieving an ACR 20 response at Week 24.

Major secondary endpoints in the order of statistical testing were:

- The change from baseline in the Disability Index of the Health Assessment Questionnaire (HAQ-DI) score at Week 24;

- The proportion of subjects (with baseline ≥3% body surface area [BSA] psoriatic involvement) who achieve a PASI 75 response at Week 24;

- The proportion of subjects with ACR 50 response at Week 24;

- The proportion of subjects with ACR 70 responses at Week 24;

- The change from baseline in total radiographic scores of the hands and feet at Week 24 (to be summarized in a later report).

Multiple additional efficacy analyses were conducted including Das28 response, dactylitis, enthesitis and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

The schedule of assessment is shown in the table below.

Protocol CNTO1275PSA3001											
Procedures and Evaluations [a]	Screen	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 40	Wk 52
Administrative											
Informed consent	X										
Pharmacogenomic research consent[b]	X										
Medical history/demographic data (including RF screening)	X										
Inclusion/exclusion criteria review	X	X									
Randomization		X									
IVRS/IWRS notification of joint scores		X				X					
Study Drug											
Study agent injection		X	X			X	X	X	X	X	X
Efficacy											
Body Surface Area (BSA)% psoriasis skin involvement		X									
PsA evaluations[c]	X	X	X	X	X	X	X	X	X	X	X
CRP	X	X	X	X	X	X	X	X	X	X	X
Dactylitis and enthesitis assessments		X						X			X
Radiographs of hands and feet		X						X			X
HAQ-DI		X	X	X	X	X	X	X	X	X	X
SF-36		X				X		X			X

Sample size

The study was powered to detect significant treatment differences in reducing the signs and symptoms of arthritis. With 600 subjects (200 subjects in each treatment group), assuming 50% MTX usage at baseline, a simulation of 5,000 repetitions was used to calculate the power to detect a significant difference in the proportion of subjects achieving an ACR 20 response using a CMH test with stratification by subjects' baseline MTX usage (yes/no). The study had over 99% power to detect the

treatment differences (α=0.05) in ACR 20 response for at least one ustekinumab group compared with the placebo group assuming the effect size of 20% to 25% for subjects not receiving MTX and 25% to 30% for subjects receiving MTX in achieving ACR 20 at Week 24. These assumptions were based on the data from the ustekinumab Phase 2 PsA study, C0743T10.

Randomisation

The randomization was stratified by investigational site, baseline weight (≤100 kg or >100 kg), and baseline MTX usage (yes/no) since these three factors could potentially affect the outcome measures. The randomization method was minimization with a biased-coin assignment in a 1:1:1 ratio, resulting in approximately 200 subjects to each group. This randomization method was chosen since some of the study sites may only enrol a few subjects and it would be difficult to ensure balanced treatment assignments within each combination of site stratum, weight stratum and baseline MTX stratum using a traditional block randomization. The randomization using the minimization with a biased coin assignment minimizes the imbalance in the distribution of the number of subjects across treatment groups within the levels of each individual stratification factor.

Blinding (masking)

At the Week 24 database lock, the data was unblinded for analysis while subjects are still participating in the study. Identification of sponsor personnel who had access to the unblinded subject-level data was documented prior to unblinding. Investigative study sites and subjects remained blinded to treatment assignment until the last subject enrolled completed the Week 108 evaluations for CNTO1275PSA3001 and the Week 60 evaluations for CNTO275PSA3002 and the respective database was locked for each study. Data that could potentially unblind the treatment assignment (i.e., study agent serum concentrations, antibodies to study agent, treatment allocation) was handled with special care to ensure that the integrity of the blind was maintained and the potential for bias was minimized. This could include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Statistical methods

All statistical tests were 2-sided and performed at α=0.05.

The primary analysis was based on all randomized subjects according to their assigned treatment groups regardless of the actual treatment received.

The proportion of subjects with ACR 20 response at Week 24 was compared between the combined ustekinumab group (45 mg group and 90 mg group combined), each individual dose group and the placebo group. The re-randomization test was used as the primary statistical testing method to determine the p-values for these comparisons. In addition, a CMH test, stratified by baseline MTX usage (yes/no), was also performed for these comparisons as a sensitivity analysis.

To maintain a Type I error rate of 0.05, the pairwise comparisons between each dose group and the placebo group were performed after the combined group showed a significant treatment effect compared with the placebo group at a significance level of 0.05.

To control for multiplicity for the primary endpoint analysis and the major secondary endpoint analyses, the 5 major secondary analyses listed below were performed sequentially contingent upon the success of the primary statistical analysis. That is, for each endpoint, the test between the combined ustekinumab group and the placebo group was performed first. If that test was significant at the 0.05 level, then the pairwise comparison between each dose group and the placebo group was performed. If at least one dose group comparison with placebo was significant at the 0.05 level, then the test for the next endpoint could be performed. Otherwise, the p-values for the subsequent

endpoints would be considered nominal. The following prespecified order was used to analyse the major secondary endpoints:

1. The change from baseline in HAQ-DI score at Week 24

2. The proportion of subjects (with baseline ≥3% BSA psoriatic involvement) who achieve a PASI 75 response at Week 24

3. The proportion of subjects with ACR 50 response at Week 24

4. The proportion of subjects with ACR 70 response at Week 24

5. The change from baseline in total radiographic scores of the hands and feet at Week 24 based on the pooled data from CNTO1275PSA3001 and CNTO1275PSA3002, which are not available yet and will be summarized in a separate report after the Week 52 DBL.

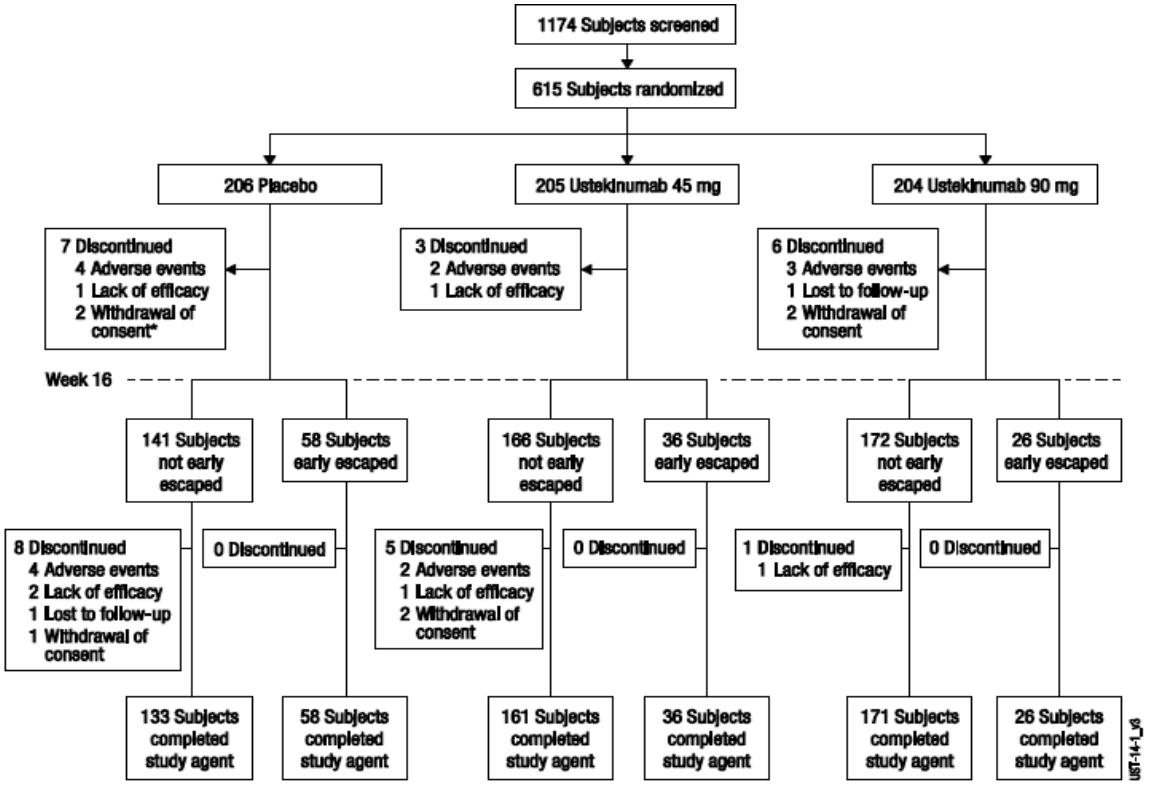
Nominal p-values were reported for all other endpoints. The ordering of the secondary endpoints prevents any problems of error inflation caused by testing multiple endpoints.

Results

Participant flow

The disposition of subjects through Week 24 is shown in Figure 7.

Figure 7: Subject Disposition through Week 24 (Study 3001)



*Includes one subject who was randomized but not treated

Recruitment

The study population comprised 615 randomized subjects in 104 sites. Sites were located in 14 countries: Austria (3 sites), Australia (5 sites), Canada (19 sites), Finland (3 sites), Germany (6 sites), Hungary (6 sites), Latvia (2 sites), Lithuania (4 sites), New Zealand (4 sites), Poland (8 sites), Russia (12 sites), Spain (3 sites), United Kingdom (6 sites) and the United States (23 sites).

The majority of the subjects were enrolled in Europe (64.6%) followed by North America (28.5%) and Asia-Pacific (7.0%) which includes subjects from New Zealand and Australia. Consent was obtained from the first subject on 30 Nov 2009. The last study-related procedure for the 24-Week CSR was performed 27 Oct 2011.

Conduct of the study

There were four amendments to the protocol. The first amendment was on 16 Oct 2009, the second was on 30 Apr 2010, the third was on 27 Oct 2010 and the fourth was on 16 Feb 2012.

Baseline data

Baseline demographics and disease characteristics were similar across treatment groups and indicative of the protocol-defined population of subjects with active PsA. The majority of randomized subjects were men (53.7%) and the median subject age was 48 years. Subjects were predominantly Caucasian (96.6%). Subjects' median weight was 86.0 kg and median body mass index (BMI) was 29.7 kg/m^2.

The most prevalent PsA subtype was polyarticular arthritis with no rheumatoid arthritis (37.9% of subjects). As commonly observed in the PsA population, the median duration of Ps (13.2 years) was substantially greater than the median duration of PsA (4.03 years).

The majority of subjects (71.5%) had at least 3% BSA involved by Ps, a median percent of BSA skin involvement of 11.0% and the median PASI score was 8.0, indicative of a study population with active Ps.

The included population had moderate to severe disease with a median numbers of swollen and tender joints of 10.0 and 20.0, respectively, a median HAQ-DI score of 1.25, and a median CRP of 10.30 mg/L.

While using the DAS28 score may be problematic in PsA with oligoarticular disease or where the lower limbs are predominantly involved, it is clear that the median DAS28 score was high.

The mean BASDAI score was >6/10 for those with spondylitis. 48.1% of subjects had dactylitis with a median score of 4.0 and 71.7% of subjects had enthesitis with a median score of 4.0. The high proportions of subjects with dactylitis/enthesitis/skin disease and to a lesser extent spondylitis, allow assessment of efficacy across the many domains of psoriatic arthritis.

Approximately half of the subjects (48.1%) were taking MTX at baseline at a median dose of 15.0 mg/week. At baseline, 15.6% of subjects were taking oral corticosteroids at median doses of 5.0 mg/day. The majority of the subjects (74.5%) were taking NSAIDs at baseline and the majority of subjects (79.5%) had prior DMARD experience. Subjects were naïve with respect to anti-TNF therapy.

Numbers analysed

Number of subjects by study treatment assigned vs. study treatment received; randomized subjects

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
Subjects randomized	206	205	204
Subjects treated	205	205	204
Treatment received			
Placebo[a]	147 (71.7%)	0	0
Early escape (placebo → 45 mg)[b]	58 (28.3%)	0	0
45 mg only[a]	0	169 (82.4%)	0
Early escape (45 mg → 90 mg)[b]	0	36 (17.6%)	0
90 mg[c]	0	0	204 (100.0%)

[a] Subjects who did not early escape at Week 16.
[b] Subjects who early escaped at Week 16.
[c] Includes all subjects irrespective of early escape.

[P_TG_7_A.rtf] [CNTO1275\DATACENTER_NA\PSA3001\DBR_WEEK_024\RE_WEEK_024_CSR\P_TG_7_A.sas] 02FEB2012, 23:24

Outcomes and estimation

Primary Efficacy Endpoint Analysis

ACR 20 Response at Week 24

At Week 24, a significantly greater proportion of subjects in the combined ustekinumab, 45 mg, and 90 mg groups (46.0%, 42.4%, 49.5%, respectively) achieved an ACR 20 response compared with subjects in the placebo group (22.8%). Both p-values by either the re-randomization test (primary analysis) or the CMH test (sensitivity analysis) were significant ($p<0.001$, Table 2). A numerically higher ACR 20 response at Week 24 was observed in the 90 mg group compared with the 45 mg group.

Table 2: Number of subjects who achieved an ACR 20 response at Week 24; randomized Subjects

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Ustekinumab Combined
Subjects randomized	206	205	204	409
ACR 20				
N	206	205	204	409
Subjects in response	47 (22.8%)	87 (42.4%)	101 (49.5%)	188 (46.0%)
p-value[a]		< 0.001	< 0.001	< 0.001
p-value[b]		< 0.001	< 0.001	< 0.001

[a] Based on CMH chi-square test.
[b] Based on re-randomization test.

[E_ACR_5_A.rtf] [CNTO1275\DATACENTER_NA\PSA3001\DBR_WEEK_024\RE_WEEK_024_CSR\e_acr_5_a.sas] 14MAY2012, 09:54

The primary endpoint was clearly met and was clinically and statistically significant.

Sensitivity analyses were conducted to test the robustness of the primary endpoint and to assess the impact of missing data. All of the sensitivity analyses showed results similar to the main analysis results, confirming efficacy and demonstrating that the conclusions were robust and not impacted by the data handling rules for missing data.

Benefit in terms of ACR 20 response at week 24 was observed in both subjects receiving MTX at baseline (26.0%, 43.4%, and 45.5% in the placebo, 45 mg, and 90 mg groups, respectively), and not

receiving MTX at baseline (20.0%, 41.5%, and 53.4% in the placebo, 45 mg, and 90 mg groups, respectively).

Major Secondary Endpoint Analyses

Improvement From Baseline in HAQ-DI Score at Week 24

There was significantly greater improvement in HAQ-DI scores at Week 24 in subjects in the combined ustekinumab and ustekinumab 45 mg and 90 mg groups (all with a median change from baseline of -0.25) compared with subjects in the placebo group (median of 0.00) by either the re-randomization test or the test of analysis on the van der Waerden normal scores (sensitivity analysis) ($p<0.001$). The mean improvement in HAQ-DI score at Week 24 was numerically higher in the 90 mg group compared with the 45 mg group.

PASI 75 Response at Week 24

In the combined, 45 mg, and 90 mg ustekinumab groups, 59.9%, 57.2%, and 62.4%, respectively, achieved a PASI 75 response compared with subjects in the placebo group (11.0%). Both p-values by either the re-randomization or CMH chi-square test (sensitivity analysis) were significant ($p <0.001$). A numerically higher PASI 75 response at Week 24 was observed in the 90 mg group compared with the 45 mg group.

ACR 50 and ACR 70 Response at Week 24

At Week 24, a significantly greater proportion of subjects in the combined ustekinumab group and in each of the individual ustekinumab groups achieved either an ACR 50 or ACR 70 response compared with the placebo group. Both p-values by either the re-randomization test or the CMH chi-square test (sensitivity analysis) were significant and consistent with the primary endpoint (<0.001). Numerically higher ACR 50 and ACR 70 responses at Week 24 were observed in the 90 mg group compared with the 45 mg group.

The primary and all major secondary endpoints were met and demonstrated clinically meaningful and statistically significant evidence of efficacy. This held for those on and those not on concomitant MTX. For most endpoints efficacy trended higher for the 90mg dose.

Other Secondary Endpoints

Other secondary analysis included the following:

ACR 20, ACR 50, and ACR 70 Responses at Week 12

At Week 12, there was a significantly greater proportion of subjects in the combined ustekinumab, 45 mg, and 90 mg groups who achieved an ACR 20 and ACR 50 response compared with subjects in the placebo group. There was a significantly greater proportion of subjects with an ACR 70 response in the combined ustekinumab and 90 mg groups ($p=0.034$ and $p=0.016$, respectively) but not in the 45 mg group ($p=0.127$) compared with the placebo group.

ACR 20, ACR 50, ACR 70 Responses Over Time by MTX Use at Baseline

Randomization was stratified by baseline MTX use. Similar number of subjects were on baseline MTX (n=200) to those not on baseline MTX (n=209). Within each MTX stratum, higher ACR 20, ACR 50 and ACR 70 responses were consistently observed over time in the ustekinumab groups than in the placebo group. In general, the trends observed for onset of response and timing of the maximum response within each MTX stratum were similar to those observed in the overall population.

A treatment effect was noted whether patients are on concomitant MTX or not, although the treatment effect is larger for those not on MTX. All efficacy results other than ACR20 in the 45 mg group trend to slightly higher values in those not on concomitant MTX. However efficacy is clearly demonstrated regardless of MTX usage and the addition of ustekinumab to those on MTX therapy increases efficacy.

ACR 20, ACR 50, ACR 70 Responses by Weight

Randomization was stratified by baseline weight (≤100 kg vs. >100kg). There were approximately 3 times as many subjects in the ≤100 kg group (n=307) as in the >100 kg group (n=102). ACR 20, 50, and 70 responses were summarized over time by weight (≤100kg and >100kg). In general, similar trends as the overall population were observed in terms of onset of action and timing of the maximum response within each weight stratum. Across all treatment groups, ACR responses generally trended higher for subjects in the ≤100 kg group especially for ACR 50 and ACR 70 responses.

The trend for higher efficacy with the 90mg dose for both weight strata and for higher efficacy in patients <100kg is consistent with the data provided for Ps and also with the PK data.

DAS28 Response Measurements

As early as Week 4, there was a notable difference in the proportion of subjects with a DAS28 response in the ustekinumab groups and the placebo group (44.5% in the 90 mg group and 42.9% in the 45 mg group achieved a DAS28 response compared with the 18.6% in the placebo group).

The proportion of subjects achieving a DAS28 response was significantly higher in both ustekinumab dose groups compared with the placebo group at both Week 12 and at Week 24 ($p<0.001$ for all comparisons). At Week 24, the proportion of subjects achieving a DAS28 response was 66.7% in the combined ustekinumab group, 65.9% in the 45 mg group, and 67.6% in the 90 mg group compared with 34.5% in the placebo group.

DAS28 Remission Over Time

DAS28 remission generally trended upward over time. DAS28 remission was achieved by a significantly greater proportion of subjects in the combined ustekinumab group and individual ustekinumab treatment groups compared with the placebo group at Week 12 and Week 24 ($p<0.001$ for all comparisons except for $p=0.002$ for 90 mg at Week 12). At Week 24, the proportion of subjects achieving DAS28 remission was 20.0% in the combined ustekinumab group, 20.5% in the 45 mg group, and 19.6% in the 90 mg group compared with 8.3% in the placebo group.

Dactylitis at Week 24

At baseline, approximately half the subjects randomized (48.1%) reported at least 1 digit with dactylitis. At Week 24, among the subjects with dactylitis at baseline, the proportion of subjects with 1 or more digits with dactylitis was significantly lower in the combined ustekinumab group (56.2%, $p=0.001$), in the 45 mg group (56.6%, $p=0.005$), and in the 90 mg (55.8%, $p=0.004$) compared with the placebo group (76.1%).

Enthesitis at Week 24

At baseline, 71.7% of the subjects randomized reported enthesitis. At Week 24, among the subjects with enthesitis at baseline, the proportion of subjects with enthesitis was statistically significantly lower in the combined ustekinumab group (64.6%, $p<0.001$), in the 45 mg group (68.6%, $p=0.018$), and in the 90 mg (60.8%, $p<0.001$) compared with the placebo group (81.0%).

Bath Ankylosing Spondylitis Disease Activity Index

At Week 12, a significantly higher proportion of subjects achieved at least a 50% improvement in BASDAI in the combined ustekinumab group and in the 45 mg group, but not in the 90 mg group

compared with the placebo group. At Week 24, a significantly higher proportion of subjects achieved at least a 50% improvement in BASDAI in the combined ustekinumab group (27.9%, p=0.023) and the 90 mg group (31.7%, p=0.014), but not in the 45 mg group (23.5%, p=0.133) compared with the placebo group (13.1%).

At both Week 12 and Week 24, a significantly higher proportion of subjects achieved at least a 70% improvement from baseline in BASDAI in the combined ustekinumab group and each of the ustekinumab dose group as compared with the placebo group. At Week 24, the proportion of subjects achieving at least a 70% improvement in BASDAI was 14.4% in the combined ustekinumab group (p=0.002), 13.7% in the 45 mg group (p=0.003), and 15.0% in the 90 mg group (p=0.002) compared with 0% in the placebo group.

A small number of subjects showed at least 90% improvement in the 90 mg group (3/59 at Week 12 and 4/60 Week 24) while no subjects in either the 45 mg group or the placebo group achieved this level of improvement at either week.

Impact of Ustekinumab on Dermatology Life Quality Index (DLQI)

The impact of ustekinumab on DLQI was assessed by comparing the change in DLQI scores from baseline for those subjects with ≥3% BSA at baseline. At Week 16 and Week 24, there was a significant improvement from baseline in DLQI score in both ustekinumab dose groups as compared with the placebo group (p<0.001). At Week 24, the median change from baseline in DLQI score was -6.00 in both ustekinumab dose groups compared with -1.00 in the placebo group.

Change From Baseline in SF-36 PCS and MCS at Week 16 and Week 24

At Week 16 and Week 24, the change from baseline in the SF-36 PCS scores was significantly greater in the combined ustekinumab group and in each of the individual ustekinumab groups compared with the placebo group (p<0.001).

At Week 16 and Week 24, the proportion of subjects that achieved a clinically meaningful improvement (≥5 from baseline in SF-36 PCS score), was significantly greater in the combined ustekinumab group and in each of the individual ustekinumab groups compared with the placebo group.

At Week 16 and Week 24, the change from baseline in the SF-36 MCS scores was significantly greater in the ustekinumab 90 mg group compared with the placebo group (p=0.018 at Week 16 and p<0.001 at Week 24). However, the comparison between the 45 mg group and the placebo group was significantly greater (p=0.005) at Week 16, but not at Week 24 (p=0.065).

Ancillary analyses

Subgroups Defined by Demographics

The study largely enrolled Caucasians and therefore cannot meaningfully assess the ustekinumab effect on other races. For subgroups by age, gender, BMI and geographic regions, across both doses as well as in the combined dose group versus the placebo group, consistent and significant treatment effect determined by ACR 20 at Week 24 has been observed across different subgroups with the exception of subjects with normal BMI and subjects from Asian Pacific region (New Zealand and Australia). The treatment effect for both doses and combined group versus placebo was smaller in subjects with normal BMI, in part due to higher placebo response rate (31.1%). The small sample size for subjects from Asian Pacific region limits the interpretation.

Efficacy Responses by Subject Weight

Randomization was stratified by baseline weight (≤100kg versus >100kg). There were approximately 3 times as many subjects in the ≤100 kg group (n=461) as in the >100 kg group (n=154).

Within each weight stratum, consistently higher ACR 20, ACR 50 and ACR 70 responses were observed over time in the ustekinumab groups compared with the placebo group. Across all treatment groups, ACR responses generally trended higher for subjects in the ≤100 kg group compared with subjects in the >100 kg group, especially for ACR 50 and ACR 70 responses. At Week 16 (trough serum ustekinumab concentrations), the proportion of subjects with an ACR 20 response in the ustekinumab 45 mg dose group decreased in both weight strata. This dip was not observed in the 90 mg dose group.

Efficacy in Subjects by Prior DMARD Use

At baseline, 79.5% of subjects had prior DMARDs exposure. DMARD-naïve subjects had a larger treatment effect compared to subjects with previous DMARD experience.

Efficacy in Subjects with Prior DMARD Use

For subjects with prior DMARD use, the primary endpoint (ACR 20 at Week 24) was consistent with the overall population. All major secondary endpoints (ACR 50 and ACR 70, PASI 75, and HAQ-DI) were also consistent with the overall population.

Efficacy and Antibodies to Ustekinumab

Subjects who were positive for antibodies to ustekinumab (6.2%) tended to have lower clinical efficacy when compared with subjects who were negative for antibodies to ustekinumab. However, antibody positivity to ustekinumab did not preclude a clinical response.

The limited number of subjects positive for antibodies to ustekinumab precludes a definitive conclusion on the impact of antibody on efficacy.

A lower effect but still a response is seen in those with ADA positivity as in the original plaque psoriasis programme.

Study CNTO1275PSA3002 (A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled trial of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNFα Agent(s))

Study CNTO1275PSA3002 was the second phase 3 trial presented in support of the indication of psoriatic arthritis.

Methods

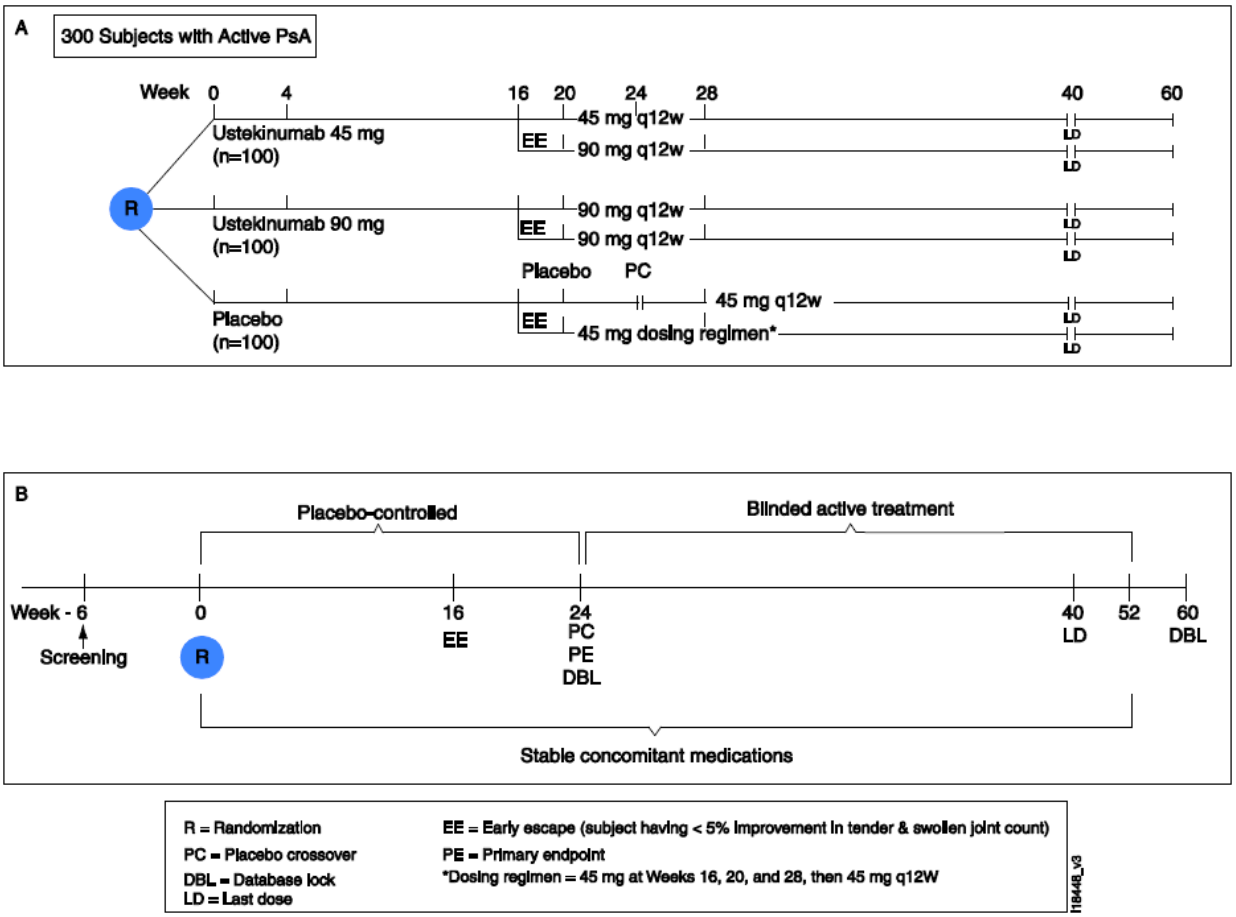
The CNTO1275PSA3002 (3002) study is a randomized, double-blind, placebo-controlled, parallel, multicenter, 3-arm study (with early escape at Week 16) of ustekinumab in subjects with PsA including those previously treated with biologic anti-TNF agent(s) (February 2010-March 2012). Approximately 300 subjects were planned to receive treatment with ustekinumab 45 mg, 90 mg, or placebo SC at Weeks 0 and 4 followed by q12w doses with the last dose at Week 40. Subjects randomized to placebo were to cross over to receive ustekinumab 45 mg at Weeks 24 and 28 followed by q12w doses with the last dose at Week 40. Subjects were to be followed for efficacy through Week 52 and for safety through Week 60. This report summarizes data included in the 24-week database lock (DBL); all PK, efficacy, and safety data through Week 24, with the exception of the radiographic data, for all randomized subjects were included in this DBL. Radiographic data through Week 52 will be available in a subsequent DBL.

The expected duration of exposure to ustekinumab for enrolled subjects is 52 weeks.

Completion of the Week 60 visit will be considered the end of the study. An additional DBL will occur at Week 60, with a future report planned to summarize the data through that time period.

The study schema through Week 60 is presented in Figure 8. The study schema for study 3002 is similar to study 3001 except that it is shorter, has fewer subjects and also includes subjects with prior anti-TNF exposure.

Figure 8: Study schema through Week 60



Study participants

As for Study CNTO1275PSA3001 except that:

At least 150 but not more than 180 subjects could have been previously treated with 1 or more biologic anti-TNF agents. Subjects previously treated with anti-TNF agents must have received at least 8 weeks of therapy with etanercept, adalimumab, golimumab, or certolizumab pegol, or at least 14 weeks of therapy with infliximab; or have documented intolerance to anti-TNF therapy for a shorter period of time. Additionally, subjects who were previously treated with anti-TNF agents and who had a history of latent TB were permitted to enrol in the study with adequate documentation about having completed appropriate treatment for latent TB within 3 years before the first administration of study agent (subjects who were anti-TNF naive were not eligible to participate if they had a previous history of latent TB).

Section 4 of the protocol contains the complete list of inclusion and exclusion criteria as well as prohibitions and restrictions to which subjects were required to adhere during the course of this study.

Treatments

Subjects were randomized to 1 of the 3 groups and received treatment with ustekinumab 45 mg, 90 mg, or placebo SC at Weeks 0 and 4 followed by q12w dosing, with the last dose at Week 40. Subjects randomized to placebo were eligible for crossover to receive ustekinumab 45 mg at Weeks 24 and 28 followed by q12w dosing, with the last dose at Week 40.

Objectives

The primary objectives of this study were to evaluate the efficacy of ustekinumab in subjects with active PsA, including those previously treated with biologic anti-TNF agent(s), by assessing the reduction in signs and symptoms of PsA and to evaluate the safety of ustekinumab in this population.

The secondary objectives of this study were to evaluate the efficacy of ustekinumab in:

- Improving physical function;
- Improving psoriatic skin lesions; and
- Inhibiting the progression of structural damage (this objective will be addressed in a future report)

Outcomes/endpoints

Primary Efficacy Endpoint Analysis

The primary endpoint was the proportion of subjects who achieved an ACR 20 response at Week 24

Major secondary endpoints and other secondary analyses were the same as for study CNTO1275PSA3001 with the additional endpoint of assessing Impact of Prior Anti-TNF Exposure on Efficacy outcomes (ACR), HAQ-DI and PASI.

Sample size

The study was powered to detect significant treatment differences in reducing the signs and symptoms of arthritis. With 300 subjects (100 subjects in each treatment group), assuming 60% MTX usage at baseline, a simulation of 5,000 repetitions was used to calculate the power to detect a significant difference in the proportion of subjects achieving an ACR 20 response using a CMH test with stratification by subjects' baseline MTX usage (yes/no). The study had over 99% power to detect the treatment differences (α=0.05) in ACR 20 response for at least one ustekinumab group compared with the placebo group, assuming an effect size of 20% to 25% for subjects not receiving MTX and 25% to 30% for subjects receiving MTX, in achieving ACR 20 at Week 24. These assumptions were based on the data from the ustekinumab Phase 2 PsA study, C0743T10.

Randomisation

Randomization was stratified by investigational site, baseline weight (≤100 kg or >100 kg), and baseline methotrexate (MTX) usage (yes/no) because these factors could have potentially affected the outcome measures. The randomization method was minimization with a biased-coin assignment (Pocock and Simon, 1975)23 in a 1:1:1 ratio, resulting in approximately 100 subjects in each group. This randomization method was chosen because some study sites might enrol only a few subjects and it would have been difficult to ensure balanced treatment assignments within each combination of site stratum, weight stratum, and baseline MTX stratum using a traditional block randomization. The

randomization using minimization with a biased-coin assignment minimizes the imbalance in the distribution of the number of subjects across treatment groups within the levels of each individual stratification factor. The measure used to calculate lack of balance in the minimization algorithm was the variance.

Blinding (masking)

Blinding was as per Study CNTO1275PSA3001

Statistical methods

All statistical tests were 2-sided and performed at $\alpha=0.05$.

The primary analysis was based on all randomized subjects according to their assigned treatment groups regardless of the actual treatment received.

The proportion of subjects with ACR 20 response at Week 24 was compared between the combined ustekinumab group (45 mg group and 90 mg group combined), each individual dose group and the placebo group. The re-randomization test was used as the primary statistical testing method to determine the p-values for these comparisons. In addition, a CMH test, stratified by baseline MTX usage (yes/no), was also performed for these comparisons as a sensitivity analysis.

To maintain a Type I error rate of 0.05, the pairwise comparisons between each dose group and the placebo group were performed after the combined group showed a significant treatment effect compared with the placebo group at a significance level of 0.05.

To control for multiplicity for the primary endpoint analysis and the major secondary endpoint analyses, the 5 major secondary analyses listed below were performed sequentially contingent upon the success of the primary statistical analysis. That is, for each endpoint, the test between the combined ustekinumab group and the placebo group was performed first. If that test was significant at the 0.05 level, then the pairwise comparison between each dose group and the placebo group was performed. If at least one dose group comparison with placebo was significant at the 0.05 level, then the test for the next endpoint could be performed. Otherwise, the p-values for the subsequent endpoints would be considered nominal. The following prespecified order was used to analyse the major secondary endpoints:

1. The change from baseline in HAQ-DI score at Week 24

2. The proportion of subjects (with baseline ≥3% BSA psoriatic involvement) who achieve a PASI 75 response at Week 24

3. The proportion of subjects with ACR 50 response at Week 24

4. The change from baseline in total radiographic scores of the hands and feet at Week 24 based on the pooled data from CNTO1275PSA3001 and CNTO1275PSA3002, which are not available yet and will be summarized in a separate report after the Week 52 DBL.

5. The proportion of subjects with ACR 70 response at Week 24

Nominal p-values were reported for all other endpoints.

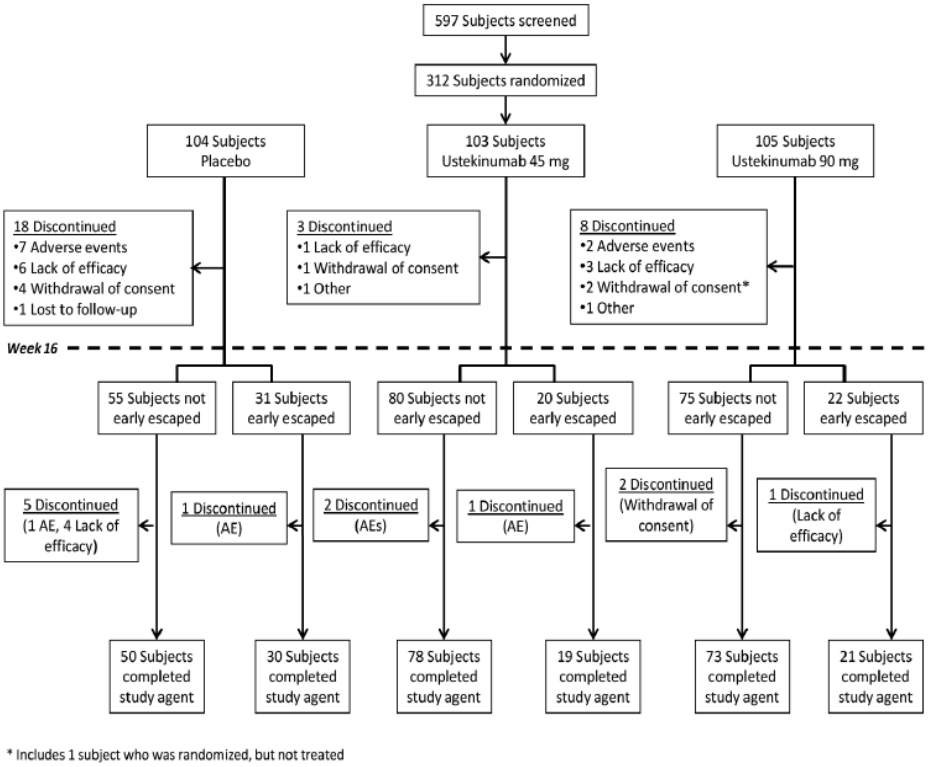
The ordering of the secondary endpoints prevents any problems of error inflation caused by testing multiple endpoints.

Data handling rules and sensitivity analyses are as for study CNTO1275PSA3001

Results

Participant flow

Figure 9: Subject Disposition through Week 24



Recruitment

The study was conducted at 71 sites in Europe and North America. Of the 597 subjects who were screened, 312 subjects were randomized into the study: 168 in Europe (53.8%) and 144 in North America (46.2%). Sites were located in 10 countries: Austria (2 sites), France (4), Germany (6), Hungary (3), Poland (5), Russia (3), Sweden (4), the United Kingdom (9), Canada (11), and the United States (24)

Conduct of the study

There were 4 amendments to the protocol, similar to those for Study CNTO1275PSA3001. The first amendment on 19 Oct 2009, the second on 30th Apr 2010, the third amendment on 27 Oct 2010 and fourth amendment on 13 Apr 2012.

Concomitant Therapy

Every effort was to be made to keep subjects on a stable concomitant medication regimen (MTX, corticosteroids, and/or NSAIDs and other analgesics) through Week 52. The investigator was permitted to reduce or temporarily discontinue the concomitant medication dose because of abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication was to be clearly documented in the subject's medical record.

Baseline data

Demographic characteristics of subjects at baseline were similar across treatment groups. Approximately half of randomized subjects were women (52.6%) and the median subject age was 49 years. Subjects were predominantly Caucasian (98.4%). Subjects' median weight was 88.3 kg and median BMI was 30.3 kg/m^2.

The baseline PsA disease characteristics for the ACR core set of outcome measurements were indicative of subjects with moderately to severely active PsA and were generally comparable across the treatment groups, with median numbers of swollen and tender joints of 11.0 and 22.0, respectively, in the overall study population. Median VAS of patient's assessment of pain was 6.80; median VAS of patient's global assessment of disease activity was 6.20; median VAS of physician's global assessment of disease activity was 7.10; median HAQ-DI score was 1.25; and median CRP level was 9.32 mg/L.

Baseline disease characteristics of psoriasis measurements for subjects with ≥3% body surface area (BSA) involvement with psoriasis were generally comparable across the treatment groups and were indicative of significant psoriatic skin involvement with a substantial negative impact on health- related quality of life (HRQoL): median percentage of BSA psoriasis skin involvement, 12%; median PASI score, 8.30; and median DLQI score, 11.00.

Of the 312 randomized subjects, 180 (57.7%) had prior anti-TNFα exposure and 132 (42.3%) were anti-TNFα naive.

At baseline, 157 (50.3%) subjects were receiving MTX and 155 (49.7%) subjects were not receiving MTX.

Through Week 24, subjects who were randomly assigned to ustekinumab received a median dose of 180 mg. Subjects randomized to placebo who entered early escape received approximately 2 ustekinumab injections, while subjects randomized to ustekinumab received an average of 3 ustekinumab injections.

Numbers analysed

Of the 312 subjects randomly assigned to treatment at Week 0, 104 were assigned to the placebo group, 103 to the ustekinumab 45 mg group, and 105 to the ustekinumab 90 mg group.

At Week 16, 73 subjects met early escape criteria: 31 (29.8%) subjects in the placebo group entered early escape and received ustekinumab 45 mg; 20 (19.4%) subjects in the ustekinumab 45 mg group entered early escape and received ustekinumab 90 mg; and 22 (21.2%) subjects in the ustekinumab 90 mg group entered early escape and continued on the same dose regimen. Most discontinuations occurred at or before Week 12, well before the reported peak effect at Weeks 20 or 24.

Discontinuation of Study Agent Through Week 24

A total of 41 (13.1%) subjects discontinued across the randomized treatment groups, with a higher rate of discontinuation in the placebo group (23.1%) than in the ustekinumab 45 mg (5.8%) or 90 mg (10.5%) groups.

Discontinuation of Study Agent for Subjects With Prior Anti-TNF Exposure

Among subjects with prior anti-TNF exposure (n=180), rates of discontinuation were higher through Week 16 and Week 24 compared with the overall population, driven by the higher proportion of

subjects who discontinued in the placebo group: 22.6% of subjects in the placebo group compared with 3.3% and 8.6% in the ustekinumab 45 mg and 90 mg groups, respectively, through Week 16, and 30.6% of subjects in the placebo group compared with 5.0% and 10.3% of subjects in the ustekinumab 45 mg and 90 mg groups, respectively, through Week 24. Similar to the overall population, the difference between the placebo group and the ustekinumab groups was primarily driven by the higher proportion of subjects in the placebo group who discontinued for efficacy-related reasons (i.e., lack of efficacy and worsening of PsA and/or Ps).

Termination of Study Participation

Through Week 24, 33 (10.6%) randomized subjects terminated their study participation. The most common reason for termination was withdrawal of consent, in 13 (12.5%) subjects in the placebo group and 12 subjects (5.8%) in the combined ustekinumab group.

Outcomes and estimation

Primary Efficacy Endpoint Analysis

ACR 20 Response at Week 24

At Week 24, a statistically significantly greater proportion of subjects in the combined ustekinumab group and in the ustekinumab 45 mg and 90 mg groups achieved an ACR 20 response (43.8%, 43.7%, and 43.8%, respectively) compared with subjects in the placebo group (20.2%; each $p<0.001$), with no evidence of dose response.

The primary endpoint was clearly met and was clinically and statistically significant.

Sensitivity analyses were conducted to test the robustness of the primary endpoint and to assess the impact of missing data. All of the sensitivity analyses showed results similar to the main analysis results, confirming efficacy demonstrating that the conclusions were robust and not impacted by the data handling rules for missing data.

Benefit in terms of ACR 20 response at week 24 was observed in both subjects receiving MTX at baseline (28.6%, 50.0%, and 40.4% in the placebo, 45 mg, and 90 mg groups, respectively), and not receiving MTX at baseline (12.7%, 36.7%, and 47.2% in the placebo, 45 mg, and 90 mg groups, respectively.

Major Secondary Endpoint Analyses

Improvement From Baseline in HAQ-DI Score at Week 24

At Week 24, the improvement from baseline in HAQ-DI score was significantly greater in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (median change from baseline of −0.25, −0.13, and −0.25, respectively) compared with the placebo group (median improvement of 0.00; all $p\leq0.002$), based on the re-randomization test [secondary analysis] or the test of analysis of covariance on the van der Waerden normal scores [sensitivity analysis])).

PASI 75 Response at Week 24

At Week 24, the proportion of subjects with ≥ 3% BSA Ps involvement at baseline who achieved a PASI 75 response was significantly greater in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (53.4%, 51.3%, and 55.6%, respectively; all $p<0.001$) compared with the

placebo group (5.0%). A numerically higher PASI 75 response at Week 24 was observed in the 90 mg group compared with the 45 mg group.

Two additional sensitivity analyses were conducted to assess the impact of missing data on this endpoint. Both sensitivity analyses showed results similar to the main analysis, demonstrating that the main analysis results were robust and not impacted by the data-handling rules for the missing data.

ACR 50 and ACR 70 Response at Week 24

At Week 24, a significantly greater proportion of subjects achieved an ACR 50 response in the ustekinumab groups compared with the placebo group. Numerically higher ACR 50 responses were observed at Week 24 in the 90 mg group compared with the 45 mg group.

The proportion of subjects who achieved an ACR 70 response at Week 24 was numerically but not significantly higher in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (7.7%, 6.8%, and 8.6 %, respectively) compared with the placebo group (2.9%).

Other Secondary Endpoints

Other secondary analysis included the following:

ACR 20, ACR 50, and ACR 70 Responses at Week 12

The proportion of subjects who achieved ACR responses at Week 12 in the combined ustekinumab group (and the ustekinumab 45 mg and 90 mg groups) versus the placebo group was as follows:

- ACR 20: 36.6% (39.6%, 33.7%) versus 17.5%

- ACR 50: 14.9% (13.9%, 15.8%) versus 4.1%

- ACR 70: 5.4% (6.9%, 4.0%) versus 1.0%

ACR 20, ACR 50, and ACR 70 Responses Over Time by MTX Use at Baseline

Among subjects treated with ustekinumab, response rates were generally comparable in subjects who were and were not receiving MTX at baseline (45.3% and 42.2%, respectively), although the treatment effect (i.e., the difference in response rates between the combined ustekinumab group and the placebo group) in ACR 20 at Week 24 was modestly greater in subjects who were not receiving MTX at baseline compared with subjects who were receiving MTX at baseline, because of the higher placebo response rate in subjects who were receiving MTX.

ACR 20, ACR 50, and ACR 70 Responses by Weight at Baseline

Randomization was stratified by baseline weight (≤100 kg vs. >100 kg). ACR responses at Week 24 in the combined ustekinumab group (and the ustekinumab 45 mg and 90 mg groups) versus the placebo group were as follows for the 2 weight stratums:

- ACR 20:
    - ≤100 kg group: 44.9% (43.2%, 46.6%) versus 23.0%
    - >100 kg group: 41.7% (44.8%, 38.7%) versus 13.3%
- ACR 50:
    - ≤100 kg group: 24.5% (20.3%, 28.8%) versus 8.1%
    - >100 kg group: 10.0% (10.3%, 9.7%) versus 3.3%

- ACR 70:
    - ≤100 kg group: 9.5% (8.1%, 11.0%) versus 4.1%
    - >100 kg group: 3.3% (3.4%, 3.2%) versus 0.0%

The response in those >100kg is less than for the lighter subjects. The expected increased efficacy at the 90mg dose is evident in the lighter groups. This is not seen for those >100kg. There were 221 subjects <100kg and only 90 subjects >100kg and the relatively small number in each dose cohort for those >100kg may have impacted on the results.

DAS28 Response Measurements

When evaluated over time, the differences in response rates between the ustekinumab groups and the placebo group were evident as early as Week 4. By the second evaluation at Week 8, more than half (54.0%) of the subjects in the combined ustekinumab group achieved a DAS28 good or moderate response, compared with 33.7% in the placebo group. The level of response was generally maintained through Week 24. Results for an LOCF analysis were similar.

Dactylitis

Of the 312 randomized subjects, 127 (40.7%) had dactylitis diagnosed at baseline. At Week 24, among subjects with dactylitis at baseline, a numerically but not significantly lower proportion of subjects in the combined ustekinumab and the ustekinumab 45 mg and 90 mg groups (61.9%, 65.2%, and 57.9%, respectively) had dactylitis compared with the placebo group (75.8%).

At Week 24, numerically but not significantly greater percentage improvements in the dactylitis score were observed in the combined ustekinumab and ustekinumab 90 mg groups (median: −46.41 and −64.58, respectively) compared with the placebo group (0.00); no difference was observed between the ustekinumab 45 mg group and the placebo group.

Enthesitis

Of the 312 randomized subjects, 221 (70.8%) had enthesitis diagnosed at baseline. At Week 24, among subjects with enthesitis at baseline, significantly lower proportions of subjects in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (72.9%, 75.7%, and 70.0%, respectively; all $p<0.05$) had enthesitis compared with the placebo group (88.2%).

Among subjects with enthesitis at baseline, a significantly greater percentage improvement in MASES score was observed at Week 24 in the combined ustekinumab and ustekinumab 90 mg groups (percent change from baseline of −45.80 [p=0.017] and −48.33 [p=0.008], respectively) compared with the placebo group (0.00). Numerically but not significantly greater percentage improvement in MASES score was observed at Week 24 for the ustekinumab 45 mg group (percent change from baseline of −33.33) compared with the placebo group.

BASDAI

The change from baseline in BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) scores was calculated at Week 12 and Week 24 only for subjects with spondylitis with peripheral joint involvement as their primary arthritic presentation of PsA at baseline and was limited by the small sample size (n=70). Among subjects with spondylitis with peripheral joint involvement at baseline, numerically greater improvement in BASDAI was noted at Week 12 and Week 24 in subjects treated with ustekinumab 45 mg or 90 mg compared with placebo, although no consistently significant differences were observed for the proportion of subjects who achieved at least 20%, 50%, or 70% improvement in

BASDAI between ustekinumab groups and the placebo group. Only 1 subject in the 90 mg group achieved at least a 90% improvement in BASDAI from baseline at Week 12 and Week 24

The efficacy results for dactylitis spondylitis and enthesitis show similar trends as in study 3001.

Impact of Ustekinumab on DLQI

The impact of ustekinumab on DLQI was assessed by comparing the change in DLQI scores from baseline for those subjects with ≥3% BSA Ps skin involvement at baseline. At Week 16 and Week 24, a statistically significant improvement from baseline in DLQI score was seen in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (all $p<0.001$). At Week 24, the median change from baseline in DLQI score was -6.00 in all ustekinumab groups compared with a median of 0.00 in the placebo group.

Change From Baseline in FACIT-F at Week 16 and Week 24

A statistically significant change from baseline in FACIT-F scores was observed at Week 24 in the combined ustekinumab group and in the ustekinumab 45 mg and 90 mg groups compared with the placebo group (median improvement, all 3.0 vs. 0.0; all $p\leq0.007$). Similarly, the percentage of subjects with clinically significant improvement in fatigue at Week 24 from baseline (≥4 points in FACIT-F) was significantly higher in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (49% for all) compared with the placebo group (25.8%; all $p<0.001$).

Ancillary analyses

Impact of Prior Anti-TNF Exposure on Efficacy

For subjects with prior anti-TNF exposure, a statistically significant difference was reached in the proportion of ACR 20 responders at Week 24 for the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (35.6%, 36.7%, and 34.5%, respectively) compared with the placebo group (14.5%; all $p<0.05$). This was also true for PASI 75 at Week 24 (47.1%, 45.5%, and 48.8%, respectively, vs. 2.0%; all $p<0.001$). For ACR 50 and ACR 70 at Week 24, however, numerically greater but not statistically significant results were noted for both ustekinumab doses in this population.

The improvement from baseline in HAQ-DI score was significantly greater in the combined ustekinumab and ustekinumab 45 mg and 90 mg groups compared with the placebo group at Week 24 ($p<0.02$ in all groups) for subjects with prior anti-TNF exposure.

Efficacy in Subjects with Prior DMARD Use

For subjects with prior DMARD use, the primary endpoint (ACR 20 at Week 24) was consistent with the overall population. All major secondary endpoints (HAQ-DI, PASI 75, and ACR 50 and ACR 70) were consistent with the overall population.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 3. Summary of Efficacy for trial CNTO1275PSA3001

Title: A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis.				
Study identifier	**CNTO1275PSA3001** EudraCT Number: 2009-012264-14			
Design	A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis.			
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	24 weeks (Primary efficacy endpoint database Lock) not applicable 108 weeks (ongoing)		
Hypothesis	Superiority of ustekinumab to placebo			
Treatment groups	placebo	Placebo, N=206 randomised, primary endpoint at week 24		
	45mg group	45mg ustekinumab at weeks 0, 4, 16, N=205 randomised, primary endpoint at week 24		
	90mg group	90mg ustekinumab at weeks 0, 4, 16, N=204 randomised, primary endpoint at week 24		
Endpoints and definitions	Primary endpoint	ACR 20	ACR 20 Response at Week 24	
	Major Secondary endpoints	HAQ-DI PASI 75 ACR 50/70	Improvement From Baseline in HAQ-DI Score at Week 24 PASI 75 Response at Week 24 ACR 50 and ACR 70 Response at Week 24	
Database lock	At week 24, 20 December 2011			
Results and analysis				
Analysis description	**Primary analysis**			
Analysis population and time point description	All randomised subjects For PASI all randomised subjects with ≥ 3% BSA psoriasis skin involvement at baseline Primary time point: Week 24			
Descriptive statistics and	Treatment group	placebo	Ustekinumab 45mg	Ustekinumab 90mg

estimate variability	Number of subjects		206	205	204
	ACR 20 response at Week 24		47 (22.8%)	87 (42.4%)	101 (49.5%)
	p-value vs. placebo			P<0.001	P<0.001
Effect estimate per comparison	Major secondary endpoints	Comparison groups	Placebo	Ustekinumab 45mg	Ustekinumab 90mg
	change from baseline HAQ-DI score at Week 24	n Median IQ range p-value vs. placebo	206 0.00 (-0.38, 0.13)	205 -0.25 (-0.63, 0.00) P<0.001	204 -0.25 (-0.75, 0.00) P<0.001
	PASI 75 response at week 24	N Response p-value vs. placebo	146 16 (11.0%)	145 83 (57.2%) P<0.001	149 93 (62.4%) P<0.001
	ACR 50 response at Week 24	N Response p-value vs. placebo	206 18 (8.7%)	205 51 (24.9%) P<0.001	204 57 (27.9%) P<0.001
	ACR 70 response at Week 24	N Response p-value vs. placebo	206 5 (2.4%)	205 25 (12.2%) P<0.001	204 29 (14.2%) P<0.001
Analysis description	The primary efficacy analysis for all endpoints was the re-randomisation test.				

Table 4. Summary of Efficacy for trial CNTO1275PSA3002

Title: A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled trial of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNFα Agent(s)				
Study identifier	CNTO1275PSA3002. PSUMMIT II. **EudraCT Number:** 2009-012265-60. **Clinical Registry No.:** CR016483			
Design	A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled trial of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNFα Agent(s)			
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		24 weeks (DBL) not applicable 60 weeks	
Hypothesis	Superiority			
Treatment groups	placebo		Placebo, N=104 randomised, primary endpoint at week 24	
	45mg group		45mg ustekinumab at weeks 0, 4, 16, N=103 randomised, primary endpoint at week 24	
	90mg group		90mg ustekinumab at weeks 0, 4, 16, N=105 randomised, primary endpoint at week 24	
Endpoints and definitions	Primary endpoint	Primary endpoint	ACR 20	
	Major Secondary endpoints	Major Secondary endpoints	Improvement From Baseline in HAQ-DI Score at Week 24 PASI 75 Response at Week 24 ACR 50 and ACR 70 Response at Week 24	
Database lock	Week 24, 19 April 2012			
Results and analysis				
Analysis description	**Primary analysis**			
Analysis population and time point description	All randomised subjects For PASI all randomised subjects with ≥ 3% BSA psoriasis skin involvement at baseline Primary time point: Week 24			
Descriptive statistics and	Treatment group	placebo	Ustekinumab 45mg	Ustekinumab 90mg

estimate variability	Number of subjects		104	103	105
	ACR 20 response at Week 24		21 (20.2%)	45 (43.7%)	46 (43.8%)
	p-value vs. placebo			P<0.001	P<0.001
Effect estimate per comparison	Major secondary endpoints	Comparison groups	Placebo	Ustekinumab 45mg	Ustekinumab 90mg
	change from baseline HAQ-DI score at Week 24	n Median IQ range p-value vs. placebo	104 0.00 (-0.13, 0.13)	103 -0.13 (-0.38, 0.00) P<0.001	105 -0.25 (-0.50, 0.00) P<0.001
	PASI 75 response at week 24	N Response p-value vs. placebo	80 4 (5.0%)	80 41 (51.3%) P<0.001	81 45 (55.6%) P<0.001
	ACR 50 response at Week 24	N Response p-value vs. placebo	104 7 (6.7%)	103 18 (17.5%) P=0.018	105 24 (22.9%) P<0.001
	ACR 70 response at Week 24	N Response p-value vs. placebo	104 3 (2.9%)	103 7 (6.8%) P=0.171	105 9 (8.6%) P=0.060
Analysis description	The primary efficacy analysis for all endpoints was the re-randomisation test.				

Analysis performed across trials (pooled analyses and meta-analysis)

A comparison of the efficacy data through Week 24 for both Phase 3 studies, including efficacy measures related to joint disease (ACR 20, ACR 50, ACR 70, DAS28, PsARC, and BASDAI) soft tissue (dactylitis and enthesitis), skin disease (PASI 75), physical function (HAQ-DI), and quality of life evaluations (DLQI and SF-36), were presented by the MAH. The comparisons are focused on an evaluation of the consistency in the overall population for the magnitude of the treatment effect compared with placebo, dose-response, and the time course of a response. Data from CNTO1275PSA3001 and CNTO1275PSA3002 were also pooled to increase the precision in the evaluation of efficacy in subpopulations. A summary of the results is provided below.

Comparison of efficacy at Week 24 as measured by primary and major secondary endpoints; randomized subjects in CNTO1275PSA3001 and CNTO1275PSA3002

	CNTO1275PSA3001				CNTO1275PSA3002			
		Ustekinumab				Ustekinumab		
	Placebo	45 mg	90 mg	Combined	Placebo	45 mg	90 mg	Combined
Subjects randomized	206	205	204	409	104	103	105	208
ACR 20								
Subjects in response	47 (22.8%)	87 (42.4%)	101 (49.5%)	188 (46.0%)	21 (20.2%)	45 (43.7%)	46 (43.8%)	91 (43.8%)
p-value		< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001
ACR 50								
Subjects in response	18 (8.7%)	51 (24.9%)	57 (27.9%)	108 (26.4%)	7 (6.7%)	18 (17.5%)	24 (22.9%)	42 (20.2%)
p-value		< 0.001	< 0.001	< 0.001		0.018	< 0.001	0.002
ACR 70								
Subjects in response	5 (2.4%)	25 (12.2%)	29 (14.2%)	54 (13.2%)	3 (2.9%)	7 (6.8%)	9 (8.6%)	16 (7.7%)
p-value		< 0.001	< 0.001	< 0.001		0.171	0.060	0.094
PASI 75								
N	146	145	149	294				
Subjects in response	16 (11.0%)	83 (57.2%)	93 (62.4%)	176 (59.9%)	4 (5.0%)	41 (51.3%)	45 (55.6%)	86 (53.4%)
p-value		< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001
Change from baseline in HAQ-DI								
Mean (SD)	-0.10 (0.390)	-0.31 (0.521)	-0.40 (0.514)	-0.36 (0.518)	-0.03 (0.380)	-0.21 (0.461)	-0.22 (0.436)	-0.21 (0.447)
Median	0.00	-0.25	-0.25	-0.25	0.00	-0.13	-0.25	-0.25
p-value		< 0.001	< 0.001	< 0.001		0.002	< 0.001	< 0.001

Adapted from:
CNTO1275PSA3001: E_ACR_5_A.rtf, 14MAY2012, 09:54; E_ACR_20_A.rtf, 14MAY2012, 09:54; E_HAQ_4_A.rtf, 14MAY2012, 09:55; E_PASI_157_A.rtf, 03FEB2012, 00:05
CNTO1275PSA3002: E_ACR_5_A.rtf, 09MAY2012, 09:39; E_ACR_20_A.rtf, 10MAY2012, 15:10; E_HAQ_4_A.rtf, 09MAY2012, 09:39; E_PASI_157_A.rtf 19APR2012, 18:37

Comparison of other efficacy measures at Week 24; randomized subjects in CNTO1275PSA3001 and CNTO1275PSA3002

	CNTO1275PSA3001				CNTO1275PSA3002			
		Ustekinumab				Ustekinumab		
	Placebo	45 mg	90 mg	Combined	Placebo	45 mg	90 mg	Combined
Subjects randomized	206	205	204	409	104	103	105	208
DAS28								
Subjects in response	71 (34.5%)	135 (65.9%)	138 (67.6%)	273 (66.7%)	31 (29.8%)	56 (54.4%)	56 (53.3%)	112 (53.8%)
p-value		< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001
PsARC								
Subjects achieving a PsARC	77 (37.4%)	115 (56.1%)	132 (64.7%)	247 (60.4%)	32 (30.8%)	57 (55.3%)	54 (51.4%)	111 (53.4%)
p-value		< 0.001	< 0.001	< 0.001		< 0.001	0.002	< 0.001
Percent change from baseline in dactylitis score								
Randomized subjects with dactylitis at baseline	96	101	99	200	38	48	41	89
N	92	99	95	194	33	46	38	84
Mean (SD)	-21.56 (64.650)	-52.27 (59.927)	-41.02 (124.947)	-46.76 (97.257)	-34.90 (45.469)	-32.19 (70.078)	-46.26 (70.610)	-38.56 (70.248)
Median	0.00	-75.00	-70.83	-72.92	0.00	0.00	-64.58	-46.41
p-value		< 0.001	< 0.001	< 0.001		0.888	0.166	0.426
Percent change from baseline in enthesitis score								
Randomized subjects with enthesitis at baseline	145	142	154	296	73	72	76	148
N	137	140	148	288	68	70	70	140
Mean (SD)	-13.30 (84.911)	-39.32 (63.018)	-47.34 (52.179)	-43.44 (57.741)	-20.63 (45.842)	-35.25 (52.855)	-43.29 (50.772)	-39.27 (51.795)
Median	0.00	-42.86	-50.00	-48.33	0.00	-33.33	-48.33	-45.80
p-value		< 0.001	< 0.001	< 0.001		0.098	0.008	0.017
Composite PASI 75 and ACR 20								
N	146	145	149	294	80	80	81	161
Subjects with both PASI 75 and ACR 20 responses	8 (5.5%)	40 (27.6%)	62 (41.6%)	102 (34.7%)	2 (2.5%)	24 (30.0%)	31 (38.3%)	55 (34.2%)
p-value		< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001
BASDAI								
N	61	51	60	111	18	26	22	46
Subjects achieving at least a 50% improvement from baseline in BASDAI	8 (13.1%)	12 (23.5%)	19 (31.7%)	31 (27.9%)	1 (5.6%)	7 (28.0%)	8 (38.1%)	15 (32.6%)
p-value		0.133	0.014	0.023		0.072	0.019	0.028

Adapted from:
CNTO1275PSA3001: E_ENTH_5_A.rtf, 03FEB2012, 00:05; E_DACT_8_A.rtf, 03FEB2012, 00:05; E_DAS_8_A.rtf, 03FEB2012, 00:05; E_PASI_158_A.rtf, 03FEB2012, 00:06; E_BASD_3_B.rtf, 03FEB2012, 00:05; E_PSAR_6_A.rtf, 03FEB2012, 00:05
CNTO1275PSA3002: E_ENTH_5_A.rtf, 19APR2012, 18:35; E_DACT_8_A.rtf, 19APR2012, 18:35; E_DAS_7_A.rtf, 19APR2012, 18:34; E_PASI_158_A.rtf, 19APR2012, 18:39; E_BASD_3_B.rtf, 19APR2012, 18:37; E_PSAR_6_A.rtf, 19APR2012, 18:34

The treatment effects for ACR 50 and ACR 70 were higher in CNTO1275PSA3001, possibly related to the fact that CNTO1275PSA3002 enrolled a more treatment refractory population with prior anti-TNFα exposure. Across both studies, 90 mg resulted in numerically higher ACR 50 and ACR 70 response rates than the 45 mg.

Both the Phase 3 study CNTO1275PSA3002 and the Phase 2 study C0743T10 enrolled subjects with previous anti-TNFα exposure. The proportion of subjects with an ACR 20 response was larger for all ustekinumab groups compared with the placebo group with or without prior biologic anti-TNFα therapy

exposure. Of note, subjects who were naïve to anti-TNFα therapy had a larger treatment effect compared with subjects who had previous anti-TNFα exposure across both C0743T10 and CNTO1275PSA3002 studies.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study C0743T10 supported proof of concept for ustekinumab in the treatment of PsA and also broadly supported the posology already licensed for plaque psoriasis (Ps).

Two well designed pivotal studies were provided in support of this extension of indication. The larger pivotal phase 3 study CNTO1275PSA3001 and the second smaller study CNTO1275PSA3002 had a similar study design. The differences were as follows:

- Study Population: in addition to the anti-TNF naïve subjects as in CNTO1275PSA3001 study, CNTO1275PSA3002 study also enrolled subjects who have been previously treated with biologic anti-TNF agent(s). At least 150, but no more than 180 of the 300 randomized subjects must have been previously treated with anti-TNF agents.
- Study Duration: the last dose in CNTO1275PSA3002 study was at Week 40. Subjects were followed for efficacy through Week 52 and safety through Week 60. Database locks occurred at Week 24 and Week 60.
- Study Size: in study CNTO1275PSA3002 approximately 300 subjects were randomly assigned to treatment with ustekinumab 45 mg, 90 mg, or placebo SC at Week 0 in this study whereas in study CNTO1275PSA3001 around 600 subjects were included.

Both studies included ~50% of patients taking concomitant MTX and assessed a large number of endpoints related to joints, heath related quality of life, dactylitis, enthesitis spondylitis and skin.

Efficacy data and additional analyses

All primary and major secondary endpoints were met and clearly demonstrated clinically and statistically significant results for both doses in both studies, with the exception of ACR 70 response in study CNTO1275PSA3002 which showed numerical improvement.

As 2 doses were used at the already licensed posology for Ps, analysis of efficacy by weight and dose was performed. Exposure in those >100kg on the 90 mg dose is similar to exposure in those <100kg on the 45mg dose. Efficacy was higher at the 90mg dose for ACR20 particularly in those >100kg in study CNTO1275PSA3001 but not for the smaller second study CNTO1275PSA3002. A relationship between exposure (serum trough levels) and weight was shown and therefore the proposed recommendation to allow for the higher 90mg dose in those >100kg is supported and is in line with the Ps licensed posology.

In study CNTO1275PSA3001, efficacy was seen in all subgroups consistent with an effect from ustekinumab across a range of baseline medications used for PsA. The included population had moderate to severe disease with a median numbers of swollen and tender joints of 10.0 and 20.0, respectively, a median HAQ-DI score of 1.25, and a median CRP of 10.30 mg/L.

While using the DAS28 score may be problematic in PsA with oligoarticular disease or where the lower limbs are predominantly involved, it is clear that the median DAS28 score was high.

The mean BASDAI score was >6/10 for those with spondylitis. 48.1% of subjects had dactylitis with a median score of 4.0 and 71.7% of subjects had enthesitis with a median score of 4.0. The high proportions of subjects with dactylitis/enthesitis/skin disease and to a lesser extent spondylitis, allows assessment of efficacy across many domains of psoriatic arthritis.

A treatment effect is noted whether patients are on concomitant MTX or not. All ACR and PASI efficacy results, other than ACR20 in the 45 mg group, trended to slightly higher values in those not on concomitant MTX. The differences in efficacy are not consistently higher or lower when comparing concomitant MTX with monotherapy. Efficacy is clearly demonstrated regardless of MTX usage.

Evidence for efficacy in each of the components of the ACR is demonstrated also showing higher efficacy at the 90mg dose. This shows that efficacy is not restricted to symptoms only, as both clinical signs (swollen joint count, dactylitis) and measures of systemic inflammation (CRP) all show a treatment effect.

Efficacy results are consistent for joints, dactylitis, enthesitis and spondylitis. A small reduction in the numbers with enthesitis is shown. The reduction in the severity of enthesitis is not as marked as seen in dactylitis. It is also noted that accurate assessment of enthesitis is difficult.

A clear exposure response relationship was observed for psoriasis, while it was less clear for PsA.

A lower effect but still a response is seen in those with ADA positivity as in the original plaque psoriasis programme. The conclusion that ADA positivity does not preclude a response is agreed.

The indication initially applied for by the MAH was as follows: “STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Stelara has been shown to improve physical function (see section 5.1)”. In line with the Guideline on Summary of Product Characteristics, the physical function claim was not included in the indication in section 4.1 but placed as an information in section 5.1.

2.4.4. Conclusions on the clinical efficacy

Efficacy for the signs and symptoms of PsA have been clearly demonstrated across a wide range of disease manifestations (joint, soft tissue) in patients who have failed previous DMARDs as well as in those who have prior anti-TNF exposure. All primary and major secondary endpoints were met and clearly demonstrated clinically and statistically significant results, with the exception of ACR 70 response in study CNTO1275PSA3002 which showed numerical improvement. Efficacy was seen whether ustekinumab was given as monotherapy or as an add-on to MTX.

2.5. Clinical safety

2.5.1. Introduction

Patient exposure

The safety of ustekinumab was evaluated in safety data pooled from the 2 ongoing, placebo-controlled Phase 3 PsA studies (CNTO1275PSA3001 and CNTO1275PSA3002). These studies have similar designs and the PsA data summarized are derived from the following 3 studies:

- CNTO1275PSA3001
    - Data through Week 24 for 615 randomized subjects as captured in the 24-Week data base lock (DBL).
    - Data through Week 52 for 356 subjects randomized prior to 26 Oct 2010 who were to have completed their Week 52 visit by the time of the 24-Week DBL (either terminated the study or completed study through Week 52). This group of subjects is referred to as the 52-Week safety subset.
- CNTO1275PSA3002
    - Data through Week 24 for 312 randomized subjects as captured in the 24-Week DBL.
- C0743T10
    - Data through Week 36 for 146 randomized subjects.

As supportive safety information, the safety of ustekinumab in PsA is compared with the safety of ustekinumab in Ps. Safety data from Ps studies are relevant for comparison for the evaluating the safety of ustekinumab in PsA for the following reasons:

- Ps and PsA commonly co-exist in the same patient, and patients with these diseases have similar comorbidities and medical risks as supported by the following:

    - Approximately 28% of the subjects in the Phase 3 Ps studies (C0743T08 and C0743T09) had a baseline medical history or current diagnosis of PsA. Similarly, approximately 75% of the subjects in the Phase 3 PsA studies (CNTO1275PSA3001 and CNTO1275PSA3002) had Ps with ≥3% body surface area (BSA) skin involvement at baseline.

    - The PsA and the Ps populations share certain risk factors such as increased cardiovascular (CV) risk, increased body weight, and increased body mass index (BMI).6;7;17

- The 2 pivotal, placebo-controlled Phase 3 Ps studies (C0743T08 and C0743T09) had similar SC dosing regimens as the 2 Phase 3 PsA studies.

Standard analyses of AEs focus on comparisons of pooled safety data from the combined Phase 3 PsA studies (CNTO1275PSA3001 and CNTO1275PSA3002) with pooled safety data from the 2 pivotal Phase 3 Ps studies (C0743T08 and C0743T09). For the analyses of less frequently occurring targeted events, pooled data from the global Ps studies (Phase 2 C0379T04 study and 3 Phase 3 studies [C0743T08, C0743T09, and C0743T12]) were used, unless otherwise stated. These studies were selected for comparison since they were conducted in generally the same geographic regions as the PsA programs and would be expected to have recruited subjects with similar demographics and comorbidities. In addition, the C0743T08 and C0743T09 studies incorporated 5-year long-term extension (LTE) phases providing supportive long-term safety data. The database for the global Ps studies includes safety information from a total of 3117 subjects with approximately 9000 subject-years of follow-up and provides extensive clinical study safety data of ustekinumab.

Supportive Safety Data from Crohn's Disease Studies

The safety of ustekinumab in Crohn's disease was considered relevant because the Crohn's disease studies provide additional safety of ustekinumab in subjects using concomitant immunosuppressant agents (e.g., corticosteroids, 5-aminosalicylic acid [5-ASA], azathioprine [AZA], and 6-mercaptopurine

[6-MP]). Moreover, safety was evaluated for higher doses of ustekinumab (up to 6 mg/kg IV) in the Crohn's disease studies than those administered in the PsA and Ps studies. For these comparisons, safety data from the 2 completed Phase 2 studies in Crohn's disease were used (C0379T07 and C0743T26, Table 5).

Table 5. Overview of Phase 2 and Phase 3 studies of ustekinumab in Ps and Crohn's disease included in the pooled datasets

Study[a] Total follow-up (Placebo- or active comparator-control period)	Data pooled for analyses of:	Study Population	Treatment Group (Number of subjects)	Phase
PSORIASIS				
C0379T04[a] 52 weeks (20 weeks)	Targeted events	Chronic moderate to severe plaque psoriasis PASI ≥12; BSA involvement ≥10%	Fixed doses: - Placebo (n=64)[b] - Placebo→90 mg single SC dose (n=47) - 45 mg single SC dose (n=64) - 90 mg single SC dose (n=64) - 45 mg weekly x 4 SC doses (n=64) - 90 mg weekly x 4 SC doses (n=64)	Phase 2 (completed)
C0743T08[a,c] (PHOENIX 1) 264 weeks (12 weeks)	Standard and Targeted events	Chronic moderate to severe plaque psoriasis PASI ≥12; BSA involvement ≥10%	Fixed doses: - Placebo (n=255) - Placebo→45 mg regimen (n=123)[c] - Placebo→90 mg regimen (n=120)[c] - 45 mg SC Weeks 0, 4 then q12w (n=255) - 90 mg SC Weeks 0, 4 then q12w (n=256)	Phase 3 (completed)
C0743T09[a,c] (PHOENIX 2) 264 weeks (12 weeks)	Standard and Targeted events	Chronic moderate to severe plaque psoriasis PASI ≥12; BSA involvement ≥10%	Fixed doses: - Placebo (n=410) - Placebo→45 mg regimen (n=197)[c] - Placebo→90 mg regimen (n=195)[c] - 45 mg SC Weeks 0, 4 then q12w (n=409) - 90 mg SC Weeks 0, 4 then q12w (n=411)	Phase 3 (completed)
C0743T12[a] (ACCEPT) 64 weeks (12 weeks)	Targeted events[e]	Chronic moderate to severe plaque psoriasis PASI ≥12; BSA involvement ≥10%	Fixed doses: - Etanercept 50 mg SC twice weekly for 12 weeks (n=347)[d] - 45 mg SC at Weeks 0, 4 (n=209)[d] - 90 mg SC at Weeks 0, 4 (n=347)[d]	Phase 3 (completed)

Study[a] Total follow-up (Placebo- or active comparator-control period)	Data pooled for analyses of:	Study Population	Treatment Group (Number of subjects)	Phase
CROHN'S DISEASE				
C0379T07 28 weeks (8 weeks in Population 1 only)	Targeted events only	(Population 1) Subjects with Crohn's disease despite 5-ASA, antibiotics, corticosteroids, and/or immunomodulators (Population 2) Open-label in subjects who failed to respond to infliximab at maximum approved dose for Crohn's disease	Population 1 (n=104) - Placebo SC (n=26) at Weeks 0, 1, 2, 3 90 mg SC at Weeks 8, 9, 10, 11 - 90 mg SC (n=25) at Weeks 0, 1, 2, 3 - Placebo IV (n=27) at Week 0 4.5 mg/kg IV at Week 8 - 4.5 mg/kg IV (n=26) at Week 0 Population 2 (n=27) - 90 mg SC (n=14) at Weeks 0, 1, 2, 3 - 4.5 mg/kg IV (n=13) at Week 0	Phase 2a (completed)
C0743T26 (CERTIFI) 36 weeks (8 weeks)	Targeted events only	Adult subjects with moderately to severely active Crohn's disease previously treated with anti-TNFα therapy.	Subjects (n=526) were initially randomized to 1 of 4 IV induction treatment groups: - Placebo (n=132) - 1 mg/kg (n=131) - 3 mg/kg (n=132) - 6 mg/kg (n=131) Based on clinical response at Week 6, subjects receiving ustekinumab were re-randomized at Week 8 to placebo or 90 mg SC at Weeks 8 and 16. Subjects in placebo group received placebo SC at Week 8 and Week 16 if they were in clinical response at Week 6 or received 270 mg SC at Week 8 followed by 90 mg SC at Week 16 if they were not in clinical response at Week 6.	Phase 2b (completed)

5-ASA=5-aminosalicylic acid; BSA=body surface area; IV=intravenous; SC=subcutaneous; PASI=Psoriasis Area and Severity Index; q12w=every 12 weeks, TNFα=tumor necrosis factor alpha.

[a] Additional details of study designs are provided in Module 5.2.

[b] At Week 20, subjects in the placebo group received a single dose of 90 mg.

[c] The placebo groups crossed over to receive 45 mg or 90 mg at Weeks 12 and 16 then q12w.

[d] Treatment after Week 12 was dependent on Physician's Global Assessment (PGA) response at Week 12 and initial treatment assignment.

[e] C0743T12 was an active comparator study and did not have a placebo control. Therefore, it is excluded in analyses of the placebo-controlled period.

Adverse events

In the combined Phase 3 PsA studies, the proportions of subjects with AEs and the types of AEs were generally comparable across all treatment groups without any clear dose response or pattern. Furthermore, there were no disproportionate increases in rates or notable changes in the patterns or types of AEs observed over time.

Through the Placebo-controlled Period

Combined Phase 3 PsA Studies

Through Week 16, the proportions of subjects with AEs after the first administration of study agent were similar across all treatment groups (47.9% in the placebo group, 48.4% in the 45 mg group, 49.4% in the 90 mg group, and 48.9% in the combined ustekinumab group).

In general, the proportions of subjects with AEs and the types of AEs were comparable across treatment groups without any clear dose response. The most frequently reported AEs (occurred in ≥2% of subjects in any group) during the placebo-controlled period are presented in Table 6.

Table 6. Number of subjects with 1 or more treatment-emergent adverse events in at least 2% of the subjects in any treatment group during the controlled portions of clinical trials by preferred term; treated subjects in Phase 3 PsA and Ps studies

	PsA (0-16 weeks) CNTO1275PSA3001 and CNTO1275PSA3002				Psoriasis (0-12 weeks) C0743T08 and C0743T09			
		Ustekinumab				Ustekinumab		
	Placebo	45 mg	90 mg	Combined	Placebo	45 mg	90 mg	Combined
Subjects treated	309	308	308	616	665	664	666	1330
Avg duration of follow-up (weeks)	15.79	16.15	16.01	16.08	12.03	12.17	12.16	12.17
Avg exposure (number of administrations)	1.96	1.99	1.97	1.98	1.98	1.99	1.99	1.99
Total number of subjects with adverse events	148 (47.9%)	149 (48.4%)	152 (49.4%)	301 (48.9%)	329 (49.5%)	365 (55.0%)	332 (49.8%)	697 (52.4%)
Preferred term								
Nasopharyngitis	13 (4.2%)	16 (5.2%)	21 (6.8%)	37 (6.0%)	51 (7.7%)	56 (8.4%)	49 (7.4%)	105 (7.9%)
Headache	6 (1.9%)	15 (4.9%)	9 (2.9%)	24 (3.9%)	23 (3.5%)	33 (5.0%)	32 (4.8%)	65 (4.9%)
Upper respiratory tract infection	14 (4.5%)	10 (3.2%)	12 (3.9%)	22 (3.6%)	30 (4.5%)	36 (5.4%)	28 (4.2%)	64 (4.8%)
Arthralgia	4 (1.3%)	9 (2.9%)	10 (3.2%)	19 (3.1%)	19 (2.9%)	21 (3.2%)	16 (2.4%)	37 (2.8%)
Nausea	2 (0.6%)	8 (2.6%)	9 (2.9%)	17 (2.8%)	8 (1.2%)	10 (1.5%)	6 (0.9%)	16 (1.2%)
Diarrhoea	3 (1.0%)	9 (2.9%)	5 (1.6%)	14 (2.3%)	12 (1.8%)	13 (2.0%)	13 (2.0%)	26 (2.0%)
Fatigue	3 (1.0%)	6 (1.9%)	6 (1.9%)	12 (1.9%)	13 (2.0%)	18 (2.7%)	18 (2.7%)	36 (2.7%)
Oropharyngeal pain	2 (0.6%)	7 (2.3%)	3 (1.0%)	10 (1.6%)	7 (1.1%)	9 (1.4%)	12 (1.8%)	21 (1.6%)
Psoriatic arthropathy	12 (3.9%)	4 (1.3%)	5 (1.6%)	9 (1.5%)	9 (1.4%)	3 (0.5%)	4 (0.6%)	7 (0.5%)
Back pain	1 (0.3%)	3 (1.0%)	5 (1.6%)	8 (1.3%)	8 (1.2%)	9 (1.4%)	14 (2.1%)	23 (1.7%)
Cough	6 (1.9%)	7 (2.3%)	1 (0.3%)	8 (1.3%)	10 (1.5%)	6 (0.9%)	7 (1.1%)	13 (1.0%)
Sinusitis	9 (2.9%)	3 (1.0%)	5 (1.6%)	8 (1.3%)	10 (1.5%)	9 (1.4%)	9 (1.4%)	18 (1.4%)
Injection site erythema	3 (1.0%)	2 (0.6%)	3 (1.0%)	5 (0.8%)	3 (0.5%)	6 (0.9%)	13 (2.0%)	19 (1.4%)

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AEs of nasopharyngitis, headache, arthralgia, nausea, diarrhoea, fatigue, oropharyngeal pain, and back pain were reported more frequently in ustekinumab-treated subjects compared with placebo-treated subjects without clear evidence of a dose response.

These AEs are generally consistent with known ADRs for ustekinumab with the exceptions of nausea and arthralgia. The >2% difference in the proportion of subjects with the PT of nausea in the combined ustekinumab and placebo groups accounts for the difference observed in the Gastrointestinal disorders SOC. Rates of nausea were >4-fold higher in ustekinumab-treated groups in the combined Phase 3 PsA studies. Rates of arthralgia were 2.5-fold higher in ustekinumab-treated groups in the combined Phase 3 PsA studies (Table 6). These data supported the determination of arthralgia and nausea as new ADRs. Dental infections was also additionally identified as a new ADR.

The absence of a dose response in terms of safety profile was demonstrated in the 5 years long-term maintenance of efficacy and safety update provided for ustekinumab in Ps (type II variation 028). In the PsA population new ADR of arthralgia, nausea and dental infections have been identified.

Through Week 24

As observed in the placebo-controlled period, the proportions of subjects with treatment-emergent AEs through Week 24 in the combined Phase 3 PsA studies were similar between placebo-treated and ustekinumab-treated subjects and between the 45 mg and 90 mg groups (55.0% in the placebo group, 54.9% in the combined ustekinumab group, 59.7% in the 45 mg group, and 58.1% in the 90 mg group; Table 7).

AEs that occurred in ≥2% of subjects in any treatment group through Week 24 are presented in Table 7. The proportions of subjects with AEs and the types of AEs were generally comparable across the ustekinumab treatment groups without any clear dose response relationship with the exception of ALT elevations which were reported in a greater proportion of subjects in the 90 mg group (2.9%) compared with the 45 mg group (1.6%). Analyses of markedly abnormal clinical chemistry values did not suggest any association between ustekinumab treatment and ALT elevation.

Table 7. Number of subjects with 1 or more treatment-emergent adverse events in at least 2% of the subjects in any treatment group through Week 24 by preferred term; treated subjects in Phase 3 PsA and Ps studies

	PsA CNTO1275PSA3001 and CNTO1275PSA3002 Ustekinumab					Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Subjects treated	309	89	308	308	705	320	315	664	666	1965
Avg duration of follow-up (weeks)	20.83	8.19	24.04	23.68	21.88	12.24	12.23	24.12	23.97	20.23
Avg exposure (number of administrations)	3.16	1.97	2.95	2.92	2.81	1.99	2.00	2.97	2.95	2.65
Total number of subjects with adverse events	170 (55.0%)	24 (27.0%)	184 (59.7%)	179 (58.1%)	387 (54.9%)	152 (47.5%)	134 (42.5%)	461 (69.4%)	455 (68.3%)	1202 (61.2%)
Preferred term										
Nasopharyngitis	17 (5.5%)	0	23 (7.5%)	28 (9.1%)	51 (7.2%)	27 (8.4%)	15 (4.8%)	83 (12.5%)	89 (13.4%)	214 (10.9%)
Upper respiratory tract infection	15 (4.9%)	5 (5.6%)	19 (6.2%)	18 (5.8%)	42 (6.0%)	11 (3.4%)	11 (3.5%)	70 (10.5%)	49 (7.4%)	141 (7.2%)
Headache	7 (2.3%)	2 (2.2%)	18 (5.8%)	11 (3.6%)	31 (4.4%)	10 (3.1%)	7 (2.2%)	42 (6.3%)	41 (6.2%)	100 (5.1%)
Arthralgia	4 (1.3%)	1 (1.1%)	12 (3.9%)	13 (4.2%)	26 (3.7%)	3 (0.9%)	4 (1.3%)	36 (5.4%)	24 (3.6%)	67 (3.4%)
Diarrhoea	4 (1.3%)	1 (1.1%)	15 (4.9%)	6 (1.9%)	22 (3.1%)	2 (0.6%)	4 (1.3%)	17 (2.6%)	19 (2.9%)	42 (2.1%)
Nausea	4 (1.3%)	1 (1.1%)	10 (3.2%)	11 (3.6%)	22 (3.1%)	7 (2.2%)	2 (0.6%)	16 (2.4%)	11 (1.7%)	36 (1.8%)
Fatigue	4 (1.3%)	0	9 (2.9%)	7 (2.3%)	16 (2.3%)	5 (1.6%)	1 (0.3%)	23 (3.5%)	18 (2.7%)	47 (2.4%)
Alanine aminotransferase increased	4 (1.3%)	0	5 (1.6%)	9 (2.9%)	14 (2.0%)	1 (0.3%)	0	3 (0.5%)	7 (1.1%)	11 (0.6%)
Hypertension	7 (2.3%)	1 (1.1%)	7 (2.3%)	6 (1.9%)	14 (2.0%)	4 (1.3%)	2 (0.6%)	20 (3.0%)	16 (2.4%)	42 (2.1%)
Psoriatic arthropathy	12 (3.9%)	0	6 (1.9%)	7 (2.3%)	13 (1.8%)	1 (0.3%)	0	9 (1.4%)	6 (0.9%)	16 (0.8%)
Oropharyngeal pain	2 (0.6%)	0	7 (2.3%)	5 (1.6%)	12 (1.7%)	1 (0.3%)	2 (0.6%)	12 (1.8%)	16 (2.4%)	31 (1.6%)
Cough	6 (1.9%)	0	8 (2.6%)	3 (1.0%)	11 (1.6%)	4 (1.3%)	4 (1.3%)	14 (2.1%)	10 (1.5%)	32 (1.6%)
Sinusitis	9 (2.9%)	0	4 (1.3%)	7 (2.3%)	11 (1.6%)	4 (1.3%)	1 (0.3%)	14 (2.1%)	23 (3.5%)	42 (2.1%)
Back pain	2 (0.6%)	0	4 (1.3%)	5 (1.6%)	9 (1.3%)	5 (1.6%)	2 (0.6%)	16 (2.4%)	21 (3.2%)	44 (2.2%)
Pain in extremity	2 (0.6%)	0	1 (0.3%)	8 (2.6%)	9 (1.3%)	0	2 (0.6%)	6 (0.9%)	6 (0.9%)	14 (0.7%)
Gastroenteritis	2 (0.6%)	0	3 (1.0%)	5 (1.6%)	8 (1.1%)	0	3 (1.0%)	18 (2.7%)	10 (1.5%)	31 (1.6%)
Influenza	1 (0.3%)	0	5 (1.6%)	3 (1.0%)	8 (1.1%)	7 (2.2%)	4 (1.3%)	15 (2.3%)	16 (2.4%)	42 (2.1%)
Pruritus	0	0	4 (1.3%)	4 (1.3%)	8 (1.1%)	1 (0.3%)	3 (1.0%)	12 (1.8%)	17 (2.6%)	33 (1.7%)
Injection site erythema	4 (1.3%)	1 (1.1%)	2 (0.6%)	4 (1.3%)	7 (1.0%)	1 (0.3%)	5 (1.6%)	13 (2.0%)	19 (2.9%)	38 (1.9%)
Psoriasis	7 (2.3%)	0	5 (1.6%)	2 (0.6%)	7 (1.0%)	0	1 (0.3%)	4 (0.6%)	9 (1.4%)	14 (0.7%)
Dizziness	2 (0.6%)	0	3 (1.0%)	0	3 (0.4%)	2 (0.6%)	1 (0.3%)	13 (2.0%)	16 (2.4%)	32 (1.6%)
Ligament sprain	1 (0.3%)	0	0	3 (1.0%)	3 (0.4%)	0	0	14 (2.1%)	4 (0.6%)	18 (0.9%)
Muscle strain	1 (0.3%)	0	1 (0.3%)	2 (0.6%)	3 (0.4%)	7 (2.2%)	2 (0.6%)	8 (1.2%)	7 (1.1%)	24 (1.2%)

[a] Subjects who early escaped at Week 16.
[b] Includes all subjects irrespective of early escape.
[c] Subjects who crossed over at Week 12.

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Through Week 52

Among the 615 randomized subjects in the CNTO1275PSA3001 study, data for 347 ustekinumab-treated subjects (52-Week safety subset) and data from 1965 ustekinumab-treated subjects in the combined the C0743T08 and C0743T09 Ps studies through Week 52 are presented. Safety data through Week 52 are not currently available for the ongoing CNTO1275PSA3002 study. Consideration should be given for the difference in group sizes when comparing the 2 populations at Week 52.

Consistent with the results through Week 24, the SOCs with the highest proportions of AEs through Week 52 were Infections and infestations (39.2% in the combined ustekinumab group) followed by the

Musculoskeletal and connective tissue disorders (13.8% in the combined ustekinumab group), and gastrointestinal disorders (12.1% in the combined ustekinumab group).

AEs that occurred in ≥5% of subjects in any treatment group through Week 52 are presented in Table 8.

Table 8. Number of subjects with 1 or more treatment-emergent adverse events in at least 5% of the subjects in any treatment group through Week 52 by preferred term; treated subjects in PsA CNTO1275PSA3001 and Phase 3 Ps studies

	PsA CNTO1275PSA3001 Ustekinumab				Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo → 45 mg[a]	45 mg[b]	90 mg[b]	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Subjects treated	109	120	118	347	320	315	664	666	1965
Avg duration of follow-up (weeks)	29.79	50.09	49.97	43.67	38.92	39.27	49.92	50.11	46.49
Avg exposure (number of administrations)	3.23	4.77	4.77	4.29	3.97	3.82	4.84	4.80	4.52
Total number of subjects with adverse events	48 (44.0%)	83 (69.2%)	76 (64.4%)	207 (59.7%)	246 (76.9%)	247 (78.4%)	566 (85.2%)	559 (83.9%)	1618 (82.3%)
Preferred term									
Nasopharyngitis	7 (6.4%)	17 (14.2%)	16 (13.6%)	40 (11.5%)	74 (23.1%)	63 (20.0%)	138 (20.8%)	149 (22.4%)	424 (21.6%)
Upper respiratory tract infection	8 (7.3%)	11 (9.2%)	10 (8.5%)	29 (8.4%)	41 (12.8%)	48 (15.2%)	127 (19.1%)	111 (16.7%)	327 (16.6%)
Arthralgia	2 (1.8%)	7 (5.8%)	7 (5.9%)	16 (4.6%)	13 (4.1%)	10 (3.2%)	51 (7.7%)	45 (6.8%)	119 (6.1%)
Headache	2 (1.8%)	10 (8.3%)	3 (2.5%)	15 (4.3%)	15 (4.7%)	17 (5.4%)	64 (9.6%)	55 (8.3%)	151 (7.7%)
Diarrhoea	1 (0.9%)	9 (7.5%)	4 (3.4%)	14 (4.0%)	5 (1.6%)	7 (2.2%)	29 (4.4%)	28 (4.2%)	69 (3.5%)
Hypertension	1 (0.9%)	8 (6.7%)	3 (2.5%)	12 (3.5%)	14 (4.4%)	12 (3.8%)	29 (4.4%)	28 (4.2%)	83 (4.2%)
Nausea	0	7 (5.8%)	4 (3.4%)	11 (3.2%)	9 (2.8%)	6 (1.9%)	19 (2.9%)	19 (2.9%)	53 (2.7%)
Gastroenteritis	2 (1.8%)	2 (1.7%)	3 (2.5%)	7 (2.0%)	9 (2.8%)	12 (3.8%)	38 (5.7%)	32 (4.8%)	91 (4.6%)
Influenza	0	4 (3.3%)	2 (1.7%)	6 (1.7%)	18 (5.6%)	13 (4.1%)	34 (5.1%)	38 (5.7%)	103 (5.2%)
Back pain	1 (0.9%)	1 (0.8%)	1 (0.8%)	3 (0.9%)	14 (4.4%)	12 (3.8%)	34 (5.1%)	38 (5.7%)	98 (5.0%)
Sinusitis	0	1 (0.8%)	1 (0.8%)	2 (0.6%)	11 (3.4%)	10 (3.2%)	32 (4.8%)	42 (6.3%)	95 (4.8%)

[a] Subjects who early escaped at Week 16 or crossed over at Week 24.
[b] Includes all subjects irrespective of early escape.
[c] Subjects who crossed over at Week 12.
Note: For CNTO1275PsA3001, only includes subjects who were randomized prior to October 26, 2010

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The proportions of subjects with AEs and the types of AEs were generally comparable across the ustekinumab treatment groups without any clear dose-responses. Overall, the types of AEs were similar to that reported at earlier time points.

Serious adverse event / deaths / other significant events

Deaths

No deaths were reported in the PsA studies through the Week 24 DBLs and through 31 May 2012 in either of the ongoing CNTO1275PSA3001 and CNTO1275PSA3002 studies. Deaths were analysed as targeted events . Through the end of the reporting period, there were no deaths in the combined PsA studies.

Other Serious Adverse Events

Through the Placebo-controlled Period Combined Phase 3 PsA Studies

Through the controlled portion of the studies, all SAEs in the PsA studies and almost all SAEs in the Ps studies (with the exceptions of 2 subjects in placebo and 2 subjects in 90 mg with cellulitis, and 2 subjects in 45 mg with intervertebral disc protrusion) occurred as single events without any notable patterns with regard to SOC, type of event, or treatment group in both the PsA and Ps populations (Table 9).

The proportions of subjects with SAEs were comparable across the placebo groups and all ustekinumab dose groups in both PsA and Ps (Table 9).

Table 9. Number of subjects with 1 or more serious treatment-emergent adverse events during the controlled portions of clinical trials by MedDRA system-organ class and preferred term; treated subjects in Phase 3 PsA and Ps studies

	PsA (0-16 weeks) CNTO1275PSA3001 and CNTO1275PSA3002				Psoriasis (0-12 weeks) C0743T08 and C0743T09			
		Ustekinumab				Ustekinumab		
	Placebo	45 mg	90 mg	Combined	Placebo	45 mg	90 mg	Combined
Subjects treated	309	308	308	616	665	664	666	1330
Avg duration of follow-up (weeks)	15.79	16.15	16.01	16.08	12.03	12.17	12.16	12.17
Avg exposure (number of administrations)	1.96	1.99	1.97	1.98	1.98	1.99	1.99	1.99
Total number of subjects with serious adverse events	9 (2.9%)	4 (1.3%)	4 (1.3%)	8 (1.3%)	10 (1.5%)	10 (1.5%)	9 (1.4%)	19 (1.4%)
System-organ class/preferred term								
Gastrointestinal disorders	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.2%)	0	0	0
Duodenitis	0	1 (0.3%)	0	1 (0.2%)	0	0	0	0
Gastroduodenitis	0	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Pancreatitis chronic	0	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Ascites	0	0	0	0	1 (0.2%)	0	0	0
Renal and urinary disorders	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	0	1 (0.2%)	0	1 (0.1%)
Renal failure acute	0	1 (0.3%)	0	1 (0.2%)	0	0	0	0
Renal injury	0	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Nephrolithiasis	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Hepatobiliary disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Cholecystitis	0	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Cholecystitis chronic	1 (0.3%)	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	2 (0.6%)	1 (0.3%)	0	1 (0.2%)	0	2 (0.3%)	0	2 (0.2%)
Spinal compression fracture	0	1 (0.3%)	0	1 (0.2%)	0	0	0	0
Clavicle fracture	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Joint dislocation	1 (0.3%)	0	0	0	0	0	0	0
Radius fracture	1 (0.3%)	0	0	0	0	0	0	0
Seroma	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Nervous system disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.3%)	0	2 (0.2%)
Syncope	0	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Cerebrovascular accident	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Cerebrovascular insufficiency	1 (0.3%)	0	0	0	0	0	0	0
Cervicobrachial syndrome	0	0	0	0	1 (0.2%)	0	0	0
Sciatica	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Psychiatric disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
Anxiety	0	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Depression	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Alcohol withdrawal syndrome	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Psychotic disorder	0	0	0	0	1 (0.2%)	0	0	0
Reproductive system and breast disorders	0	1 (0.3%)	0	1 (0.2%)	0	0	0	0
Cervical polyp	0	1 (0.3%)	0	1 (0.2%)	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	1 (0.3%)	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
Erythrodermic psoriasis	0	0	1 (0.3%)	1 (0.2%)	0	0	0	0
Pityriasis rubra pilaris	0	0	0	0	1 (0.2%)	0	0	0
Psoriasis	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cardiac disorders	1 (0.3%)	0	0	0	0	1 (0.2%)	3 (0.5%)	4 (0.3%)
Angina pectoris	1 (0.3%)	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Congestive cardiomyopathy	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Coronary artery disease	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Palpitations	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Ventricular extrasystoles	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Ear and labyrinth disorders	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Vertigo	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions	1 (0.3%)	0	0	0	1 (0.2%)	0	0	0
Chest pain	0	0	0	0	1 (0.2%)	0	0	0
Pyrexia	1 (0.3%)	0	0	0	0	0	0	0
Infections and infestations	0	0	0	0	3 (0.5%)	0	3 (0.5%)	3 (0.2%)
Cellulitis	0	0	0	0	2 (0.3%)	0	2 (0.3%)	2 (0.2%)
Herpes zoster	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Pneumonia	0	0	0	0	1 (0.2%)	0	0	0
Metabolism and nutrition disorders	1 (0.3%)	0	0	0	0	0	0	0

Table 9. Number of subjects with 1 or more serious treatment-emergent adverse events during the controlled portions of clinical trials by MedDRA system-organ class and preferred term; treated subjects in Phase 3 PsA and Ps studies

	PsA (0-16 weeks) CNTO1275PSA3001 and CNTO1275PSA3002				Psoriasis (0-12 weeks) C0743T08 and C0743T09			
		Ustekinumab				Ustekinumab		
	Placebo	45 mg	90 mg	Combined	Placebo	45 mg	90 mg	Combined
Hyperglycaemia	1 (0.3%)	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.3%)	0	0	0	1 (0.2%)	3 (0.5%)	0	3 (0.2%)
Dactylitis	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Foot deformity	1 (0.3%)	0	0	0	0	0	0	0
Intervertebral disc protrusion	0	0	0	0	0	2 (0.3%)	0	2 (0.2%)
Psoriatic arthropathy	0	0	0	0	1 (0.2%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
Hepatic neoplasm malignant	0	0	0	0	1 (0.2%)	0	0	0
Meningioma benign	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	0	0	0	1 (0.2%)	0	0	0
Asthma	0	0	0	0	1 (0.2%)	0	0	0
Interstitial lung disease	1 (0.3%)	0	0	0	0	0	0	0
Vascular disorders	1 (0.3%)	0	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.2%)
Hypertension	1 (0.3%)	0	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.2%)

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Through Week 24

PsA Compared with Ps

The proportions of subjects with SAEs were comparable in the ustekinumab 45 mg and 90 mg dose groups in the psoriasis studies with no disproportionate increases in the proportions of subjects with SAEs compared with the placebo-controlled period (Table 10).

Consistent with results during the placebo-controlled portion of the studies, through Week 24 the majority of SAEs occurred as single events without any notable patterns with regard to SOC, type of event, or treatment group in both the PsA and Ps populations (Table 10).

Table 10. Number of subjects with 1 or more serious treatment-emergent adverse events through Week 24 by MedDRA system-organ class and preferred term; treated subjects in Phase 3 PsA and Ps studies

	PsA CNTO1275PSA3001 and CNTO1275PSA3002 Ustekinumab					Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Subjects treated	309	89	308	308	705	320	315	664	666	1965
Avg duration of follow-up (weeks)	20.83	8.19	24.04	23.68	21.88	12.24	12.23	24.12	23.97	20.23
Avg exposure (number of administrations)	3.16	1.97	2.95	2.92	2.81	1.99	2.00	2.97	2.95	2.65
Total number of subjects with serious adverse events	10 (3.2%)	2 (2.2%)	6 (1.9%)	5 (1.6%)	13 (1.8%)	7 (2.2%)	2 (0.6%)	21 (3.2%)	13 (2.0%)	43 (2.2%)
System-organ class/preferred term										
Gastrointestinal disorders	0	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)	0	2 (0.3%)	0	3 (0.2%)
Duodenitis	0	0	1 (0.3%)	0	1 (0.1%)	0	0	0	0	0
Gastroduodenitis	0	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0	0
Pancreatitis chronic	0	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0	0
Abdominal hernia obstructive	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Abdominal pain	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Abdominal pain upper	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Diverticular perforation	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Nervous system disorders	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)	0	3 (0.5%)	1 (0.2%)	6 (0.3%)
Cerebrovascular accident	0	0	1 (0.3%)	0	1 (0.1%)	1 (0.3%)	0	1 (0.2%)	0	2 (0.1%)
Syncope	0	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0	0
Cerebrovascular insufficiency	1 (0.3%)	0	0	0	0	0	0	0	0	0
Chorea	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Facial paresis	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Headache	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Sciatica	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Psychiatric disorders	2 (0.6%)	1 (1.1%)	0	1 (0.3%)	2 (0.3%)	1 (0.3%)	0	1 (0.2%)	2 (0.3%)	4 (0.2%)
Anxiety	0	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0	0
Depression	2 (0.6%)	0	0	1 (0.3%)	1 (0.1%)	0	0	1 (0.2%)	0	1 (0.1%)
Suicidal ideation	1 (0.3%)	1 (1.1%)	0	0	1 (0.1%)	0	0	0	0	0

Approved, Date 06 Nov 2012

Table 10. Number of subjects with 1 or more serious treatment-emergent adverse events through Week 24 by MedDRA system-organ class and preferred term; treated subjects in Phase 3 PsA and Ps studies

	PsA CNTO1275PSA3001 and CNTO1275PSA3002 Ustekinumab					Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Alcohol withdrawal syndrome	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Schizophrenia	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Suicide attempt	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Renal and urinary disorders	0	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
Renal failure acute	0	0	1 (0.3%)	0	1 (0.1%)	0	0	0	0	0
Renal injury	0	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0	0
Nephrolithiasis	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Renal failure	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Reproductive system and breast disorders	0	1 (1.1%)	1 (0.3%)	0	2 (0.3%)	0	0	0	0	0
Benign prostatic hyperplasia	0	1 (1.1%)	0	0	1 (0.1%)	0	0	0	0	0
Cervical polyp	0	0	1 (0.3%)	0	1 (0.1%)	0	0	0	0	0
General disorders and administration site conditions	1 (0.3%)	0	1 (0.3%)	0	1 (0.1%)	1 (0.3%)	0	0	0	1 (0.1%)
Device breakage	0	0	1 (0.3%)	0	1 (0.1%)	0	0	0	0	0
Chest pain	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Pyrexia	1 (0.3%)	0	0	0	0	0	0	0	0	0
Hepatobiliary disorders	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	0	0	1 (0.2%)	0	1 (0.1%)
Cholecystitis	0	0	0	1 (0.3%)	1 (0.1%)	0	0	1 (0.2%)	0	1 (0.1%)
Cholecystitis chronic	1 (0.3%)	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	2 (0.6%)	0	1 (0.3%)	0	1 (0.1%)	1 (0.3%)	0	2 (0.3%)	1 (0.2%)	4 (0.2%)
Spinal compression fracture	0	0	1 (0.3%)	0	1 (0.1%)	0	0	0	0	0
Clavicle fracture	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Joint dislocation	1 (0.3%)	0	0	0	0	0	0	0	0	0
Nerve injury	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Open fracture	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Radius fracture	1 (0.3%)	0	0	0	0	0	0	0	0	0
Seroma	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)

	PsA CNTO1275PSA3001 and CNTO1275PSA3002 Ustekinumab					Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Musculoskeletal and connective tissue disorders	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	1 (0.3%)	0	5 (0.8%)	0	6 (0.3%)
Arthritis	0	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0	0
Dactylitis	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Foot deformity	1 (0.3%)	0	0	0	0	0	0	0	0	0
Intervertebral disc degeneration	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Intervertebral disc protrusion	0	0	0	0	0	0	0	2 (0.3%)	0	2 (0.1%)
Osteoarthritis	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Pain in extremity	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Skin and subcutaneous tissue disorders	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	0	0	0	1 (0.2%)	1 (0.1%)
Erythrodermic psoriasis	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	0	0	0	0	0
Psoriasis	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cardiac disorders	1 (0.3%)	0	0	0	0	0	0	3 (0.5%)	4 (0.6%)	7 (0.4%)
Angina pectoris	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Angina unstable	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Congestive cardiomyopathy	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Coronary artery disease	0	0	0	0	0	0	0	1 (0.2%)	2 (0.3%)	3 (0.2%)
Myocardial infarction	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Palpitations	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Ventricular extrasystoles	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Ventricular tachycardia	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Ear and labyrinth disorders	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Vertigo	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Endocrine disorders	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Goitre	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)

Table 10. Number of subjects with 1 or more serious treatment-emergent adverse events through Week 24 by MedDRA system-organ class and preferred term; treated subjects in Phase 3 PsA and Ps studies

	PsA CNTO1275PSA3001 and CNTO1275PSA3002 Ustekinumab					Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Infections and infestations	0	0	0	0	0	1 (0.3%)	0	1 (0.2%)	4 (0.6%)	6 (0.3%)
Cellulitis	0	0	0	0	0	0	0	0	2 (0.3%)	2 (0.1%)
Herpes zoster	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Meningitis aseptic	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Osteomyelitis	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Sepsis	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Wound infection staphylococcal	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Investigations	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Blood pressure increased	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Metabolism and nutrition disorders	1 (0.3%)	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Hyperglycaemia	1 (0.3%)	0	0	0	0	0	0	0	0	0
Hypokalaemia	0	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Meningioma benign	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	0	0	0	0	1 (0.3%)	1 (0.3%)	0	1 (0.2%)	3 (0.2%)
Dyspnoea	0	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Interstitial lung disease	1 (0.3%)	0	0	0	0	0	0	0	0	0
Nasal congestion	0	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Respiratory failure	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Vascular disorders	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
Hypertension	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)

[a] Subjects who early escaped at Week 16.
[b] Includes all subjects irrespective of early escape.
[c] Subjects who crossed over at Week 12.

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Through Week 52

Phase 3 CNTO1275PSA3001 PsA Study

Through Week 52 in the CNTO1275PSA3001 52-Week safety subset, SAEs occurred in 4.6% (16 subjects) of subjects with available data in the combined ustekinumab group (Table 11). The proportion of subjects with treatment-emergent SAEs was higher in the 45 mg treatment group (5.8% [7 subjects, all of which occurred in subjects randomized to 45mg and not in those who early escaped]), compared with the 90 mg treatment group (2.5% [3 subjects]) although the overall incidence was low. Consistent with results through Week 24, the majority of SAEs occurred as single events without any notable patterns with regard to SOC, type of event, or treatment group.

Table 11. Number of subjects with 1 or more serious treatment-emergent adverse events through Week 52 by MedDRA system-organ class and preferred term; treated subjects in PsA CNTO1275PSA3001 and Phase 3 Ps studies

	PsA CNTO1275PSA3001 Ustekinumab				Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo → 45 mg[a]	45 mg[b]	90 mg[b]	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Subjects treated	109	120	118	347	320	315	664	666	1965
Avg duration of follow-up (weeks)	29.79	50.09	49.97	43.67	38.92	39.27	49.92	50.11	46.49
Avg exposure (number of administrations)	3.23	4.77	4.77	4.29	3.97	3.82	4.84	4.80	4.52
Total number of subjects with serious adverse events	6 (5.5%)	7 (5.8%)	3 (2.5%)	16 (4.6%)	17 (5.3%)	11 (3.5%)	37 (5.6%)	29 (4.4%)	94 (4.8%)
System-organ class/preferred term									
Cardiac disorders	3 (2.8%)	0	0	3 (0.9%)	0	3 (1.0%)	7 (1.1%)	5 (0.8%)	15 (0.8%)
Atrial fibrillation	1 (0.9%)	0	0	1 (0.3%)	0	0	0	0	0
Cardiac failure congestive	1 (0.9%)	0	0	1 (0.3%)	0	0	0	0	0
Myocardial infarction	1 (0.9%)	0	0	1 (0.3%)	0	1 (0.3%)	2 (0.3%)	0	3 (0.2%)
Acute myocardial infarction	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Angina pectoris	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Angina unstable	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Congestive cardiomyopathy	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Coronary artery disease	0	0	0	0	0	2 (0.6%)	3 (0.5%)	3 (0.5%)	8 (0.4%)
Palpitations	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Tachycardia	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Ventricular extrasystoles	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Ventricular tachycardia	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Hepatobiliary disorders	1 (0.9%)	1 (0.8%)	1 (0.8%)	3 (0.9%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.2%)	5 (0.3%)
Cholecystitis	1 (0.9%)	0	1 (0.8%)	2 (0.6%)	1 (0.3%)	0	1 (0.2%)	0	2 (0.1%)
Cholecystitis acute	0	1 (0.8%)	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (0.1%)
Biliary colic	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cholelithiasis	0	0	0	0	0	1 (0.3%)	0	1 (0.2%)	2 (0.1%)
Vascular disorders	1 (0.9%)	1 (0.8%)	1 (0.8%)	3 (0.9%)	0	0	2 (0.3%)	2 (0.3%)	4 (0.2%)
Hypertension	1 (0.9%)	1 (0.8%)	0	2 (0.6%)	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)

	PsA CNTO1275PSA3001 Ustekinumab				Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo → 45 mg[a]	45 mg[b]	90 mg[b]	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Deep vein thrombosis	0	0	1 (0.8%)	1 (0.3%)	0	0	0	0	0
Arterial occlusive disease	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Malignant hypertension	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Infections and infestations	0	1 (0.8%)	1 (0.8%)	2 (0.6%)	4 (1.3%)	0	2 (0.3%)	9 (1.4%)	15 (0.8%)
Pharyngolaryngeal abscess	0	0	1 (0.8%)	1 (0.3%)	0	0	0	0	0
Salpingitis	0	1 (0.8%)	0	1 (0.3%)	0	0	0	0	0
Appendicitis perforated	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Cellulitis	0	0	0	0	0	0	0	3 (0.5%)	3 (0.2%)
Diverticulitis	0	0	0	0	1 (0.3%)	0	0	2 (0.3%)	3 (0.2%)
Erysipelas	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Genitourinary tract infection	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Herpes zoster	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Infectious peritonitis	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Meningitis aseptic	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Osteomyelitis	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
Pneumonia	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Sepsis	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Viral infection	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Wound infection staphylococcal	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Reproductive system and breast disorders	1 (0.9%)	1 (0.8%)	0	2 (0.6%)	0	0	0	1 (0.2%)	1 (0.1%)
Benign prostatic hyperplasia	1 (0.9%)	0	0	1 (0.3%)	0	0	0	0	0
Cervical polyp	0	1 (0.8%)	0	1 (0.3%)	0	0	0	0	0
Ovarian torsion	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorders	0	0	1 (0.8%)	1 (0.3%)	2 (0.6%)	0	2 (0.3%)	2 (0.3%)	6 (0.3%)
Gastroduodenitis	0	0	1 (0.8%)	1 (0.3%)	0	0	0	0	0
Pancreatitis chronic	0	0	1 (0.8%)	1 (0.3%)	0	0	0	0	0

Table 11. Number of subjects with 1 or more serious treatment-emergent adverse events through Week 52 by MedDRA system-organ class and preferred term; treated subjects in PsA CNTO1275PSA3001 and Phase 3 Ps studies

	PsA CNTO1275PSA3001 Ustekinumab				Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo → 45 mg[a]	45 mg[b]	90 mg[b]	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Abdominal hernia obstructive	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Abdominal pain	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Abdominal pain upper	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Diverticular perforation	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Diverticulum	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Gastrooesophageal reflux disease	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Pancreatitis	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Injury, poisoning and procedural complications	0	1 (0.8%)	0	1 (0.3%)	1 (0.3%)	0	4 (0.6%)	1 (0.2%)	6 (0.3%)
Spinal compression fracture	0	1 (0.8%)	0	1 (0.3%)	0	0	0	0	0
Anaesthetic complication	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Clavicle fracture	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Nerve injury	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Open fracture	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Post procedural haemorrhage	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Seroma	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Metabolism and nutrition disorders	1 (0.9%)	0	0	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)	3 (0.2%)
Dehydration	1 (0.9%)	0	0	1 (0.3%)	0	0	0	0	0
Hypocalcaemia	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Hypokalaemia	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Obesity	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	0	1 (0.8%)	0	1 (0.3%)	2 (0.6%)	0	5 (0.8%)	0	7 (0.4%)
Finger deformity	0	1 (0.8%)	0	1 (0.3%)	0	0	0	0	0
Dactylitis	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Flank pain	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)

	PsA CNTO1275PSA3001 Ustekinumab				Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo → 45 mg[a]	45 mg[b]	90 mg[b]	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Intervertebral disc degeneration	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Intervertebral disc protrusion	0	0	0	0	1 (0.3%)	0	2 (0.3%)	0	3 (0.2%)
Osteoarthritis	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Pain in extremity	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.8%)	0	1 (0.3%)	1 (0.3%)	0	4 (0.6%)	2 (0.3%)	7 (0.4%)
Uterine leiomyoma	0	1 (0.8%)	0	1 (0.3%)	0	0	0	0	0
Breast cancer	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Glomus tumour	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Meningioma benign	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Prostate cancer	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Thyroid cancer	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Tongue neoplasm malignant stage unspecified	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Transitional cell carcinoma	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Renal and urinary disorders	0	1 (0.8%)	0	1 (0.3%)	0	0	4 (0.6%)	2 (0.3%)	6 (0.3%)
Renal failure acute	0	1 (0.8%)	0	1 (0.3%)	0	0	0	0	0
Calculus ureteric	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Nephrolithiasis	0	0	0	0	0	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Renal colic	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Renal failure	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.8%)	0	1 (0.3%)	3 (0.9%)	1 (0.3%)	1 (0.2%)	1 (0.2%)	6 (0.3%)
Asthma	0	1 (0.8%)	0	1 (0.3%)	0	0	0	0	0
Acute respiratory distress syndrome	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Aspiration	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Dyspnoea	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Nasal congestion	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)

Table 11. Number of subjects with 1 or more serious treatment-emergent adverse events through Week 52 by MedDRA system-organ class and preferred term; treated subjects in PsA CNTO1275PSA3001 and Phase 3 Ps studies

	PsA CNTO1275PSA3001 Ustekinumab				Psoriasis C0743T08 and C0743T09 Ustekinumab				
	Placebo → 45 mg[a]	45 mg[b]	90 mg[b]	Combined	Placebo → 45 mg[c]	Placebo → 90 mg[c]	45 mg	90 mg	Combined
Pneumonitis	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Pulmonary embolism	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Respiratory failure	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Ear and labyrinth disorders	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Vertigo	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Endocrine disorders	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Goitre	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Eye disorders	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Vitreous haemorrhage	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
General disorders and administration site conditions	0	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.5%)	6 (0.3%)
Chest pain	0	0	0	0	1 (0.3%)	0	1 (0.2%)	3 (0.5%)	5 (0.3%)
Cyst	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Immune system disorders	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Drug hypersensitivity	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Investigations	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Blood pressure increased	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Nervous system disorders	0	0	0	0	2 (0.6%)	3 (1.0%)	5 (0.8%)	1 (0.2%)	11 (0.6%)
Benign intracranial hypertension	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Cerebrovascular accident	0	0	0	0	1 (0.3%)	0	1 (0.2%)	0	2 (0.1%)
Chorea	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Complicated migraine	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Dizziness	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Facial paresis	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Headache	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Sciatica	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Syncope	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
VIIth nerve paralysis	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Pregnancy, puerperium and perinatal conditions	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Abortion spontaneous	0	0	0	0	0	1 (0.3%)	0	0	1 (0.1%)
Psychiatric disorders	0	0	0	0	3 (0.9%)	0	1 (0.2%)	2 (0.3%)	6 (0.3%)
Alcohol withdrawal syndrome	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Delirium	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Depression	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)
Panic attack	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Schizophrenia	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Suicide attempt	0	0	0	0	1 (0.3%)	0	0	0	1 (0.1%)
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Psoriasis	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

[a] Subjects who early escaped at Week 16 or crossed over at Week 24.
[b] Includes all subjects irrespective of early escape.
[c] Subjects who crossed over at Week 12.
Note: For CNTO1275PsA3001, only includes subjects who were randomized prior to October 26, 2010

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Laboratory findings

Haematology

In the combined PsA studies, markedly abnormal changes in haematology laboratory values were generally infrequent with comparable rates among the treatment groups through Week 16 without any dose-related or clinically-concerning patterns.

Consistent with results during the placebo-controlled period, markedly abnormal changes in haematology laboratory values through Week 24 in the combined psoriasis studies were generally infrequent occurring in comparable proportions of subjects among the treatment groups without any dose-related or clinically-concerning patterns.

Through Week 52 in the CNTO1275PSA3001 52-Week safety subset, markedly abnormal changes in haematology laboratory values remained generally infrequent with comparable types as observed through Week 24 and comparable rates among the treatment groups without any dose-related or clinically-concerning patterns.

Clinical Chemistry

In the combined PsA studies, markedly abnormal changes in chemistry laboratory values were generally infrequent with comparable rates among the treatment groups through Week 16 without any dose-related or clinically-concerning patterns In the combined PsA studies, markedly abnormal changes in chemistry laboratory values were generally infrequent with comparable rates among the treatment groups through Week 24 without any dose-related or clinically-concerning patterns.

Through Week 52 in the CNTO1275PSA3001 52-Week safety subset, markedly abnormal changes in chemistry laboratory values remained generally infrequent with comparable types as observed through Week 24. The number of subjects with events did not increase disproportionately, and the proportions of subjects with events were comparable between the 45 mg and 90 mg groups without any dose-related or clinically-concerning patterns

Immunological events

Serious Hypersensitivity Reactions (Including Anaphylaxis and Serum Sickness)

There were no subjects who experienced anaphylaxis or serum sickness reactions in the CNTO1275PSA3001 and CNTO1275PSA3002 studies through Week 24.

In the CNTO1275PSA3001 study, none of the ustekinumab injections in subjects who were positive for antibodies to ustekinumab were associated with an injection-site reaction, while 10 of 1671 (0.6%) ustekinumab injections in subjects who were negative for antibodies to ustekinumab were associated with an injection-site reaction (all mild).

In the CNTO1275PSA3002 study, none of the ustekinumab injections in subjects who were positive for antibodies to ustekinumab were associated with an injection-site reaction, while 7 of 602 (1.2%) ustekinumab injections in subjects who were negative for antibodies to ustekinumab were associated with injection-site reactions (all mild).

Therefore, there was no apparent association between the development of antibodies to ustekinumab and the occurrence of injection-site reactions in the Phase 3 PsA studies.

Safety related to drug-drug interactions and other interactions

The overall numbers of subjects with serious adverse event (SAEs) in CNTO1275PSA3001 and CNTO1275PSA3002 through Week 24 were low. Among ustekinumab-treated subjects, the proportion of subjects with 1 or more SAEs through Week 24 was similar between subjects receiving concomitant MTX and those without concomitant MTX (1.8% vs. 1.9%, respectively). A higher proportion of placebo-treated subjects reported an SAE in the concomitant MTX group (4.8%) compared with the non-concomitant MTX group (1.8%).

To evaluate whether there is a difference in the types of SAEs that occurred between subjects treated with concomitant MTX vs. those who received ustekinumab monotherapy, a summary table is provided that presents the proportions of subjects with 1 or more SAEs through Week 24 for subjects with or without concomitant MTX by MedDRA system-organ class and preferred term (PT). Within subgroups of subjects with or without concomitant MTX, SAEs occurred as single events in each treatment group, without any notable patterns with regard to SOC, type of event, or treatment group. The only SOCs with SAEs occurring in more than 1 subject in a treatment group were the Gastrointestinal disorders SOC (2 [0.6%] ustekinumab-treated subjects who were receiving concomitant MTX), the Nervous system orders SOC (2 [0.5%] ustekinumab-treated subjects without concomitant MTX), and the Psychiatric disorders SOC (2 [0.5%] ustekinumab-treated subjects without concomitant MTX). Additionally, there were no differences observed between the 45 mg and 90 mg groups, regardless of baseline MTX stat.

Attachment 19 Number of subjects with 1 or more treatment-emergent serious adverse events through Week 24 by MedDRA system-organ class and preferred term and by baseline MTX usage; treated subjects in PsA CNTO1275PSA3001 and CNTO1275PSA3002 studies

	Receiving MTX at Baseline					Not Receiving MTX at Baseline				
		Ustekinumab					Ustekinumab			
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined
Subjects treated	145	35	153	152	340	164	54	155	156	365
Avg duration of follow-up (weeks)	21.44	8.38	24.05	23.48	22.18	20.29	8.08	24.03	23.88	21.60
Avg exposure (number of administrations)	3.30	1.94	2.95	2.90	2.82	3.03	1.98	2.95	2.93	2.80
Total number of subjects with serious adverse events	7 (4.8%)	0	4 (2.6%)	2 (1.3%)	6 (1.8%)	3 (1.8%)	2 (3.7%)	2 (1.3%)	3 (1.9%)	7 (1.9%)
System-organ class/preferred term										
Gastrointestinal disorders	0	0	1 (0.7%)	1 (0.7%)	2 (0.6%)	0	0	0	0	0
Gastroduodenitis	0	0	0	1 (0.7%)	1 (0.3%)	0	0	0	0	0
Pancreatitis chronic	0	0	0	1 (0.7%)	1 (0.3%)	0	0	0	0	0
Duodenitis	0	0	1 (0.7%)	0	1 (0.3%)	0	0	0	0	0
Hepatobiliary disorders	1 (0.7%)	0	0	1 (0.7%)	1 (0.3%)	0	0	0	0	0
Cholecystitis	0	0	0	1 (0.7%)	1 (0.3%)	0	0	0	0	0
Cholecystitis chronic	1 (0.7%)	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (0.7%)	0	0	1 (0.7%)	1 (0.3%)	0	0	0	0	0
Erythrodermic psoriasis	1 (0.7%)	0	0	1 (0.7%)	1 (0.3%)	0	0	0	0	0
Cardiac disorders	1 (0.7%)	0	0	0	0	0	0	0	0	0
Angina pectoris	1 (0.7%)	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions	1 (0.7%)	0	0	0	0	0	0	1 (0.6%)	0	1 (0.3%)
Device breakage	0	0	0	0	0	0	0	1 (0.6%)	0	1 (0.3%)
Pyrexia	1 (0.7%)	0	0	0	0	0	0	0	0	0

Attachment 19 Number of subjects with 1 or more treatment-emergent serious adverse events through Week 24 by MedDRA system-organ class and preferred term and by baseline MTX usage; treated subjects in PsA CNTO1275PSA3001 and CNTO1275PSA3002 studies

	Receiving MTX at Baseline Ustekinumab					Not Receiving MTX at Baseline Ustekinumab				
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined
Injury, poisoning and procedural complications	1 (0.7%)	0	1 (0.7%)	0	1 (0.3%)	1 (0.6%)	0	0	0	0
Joint dislocation	0	0	0	0	0	1 (0.6%)	0	0	0	0
Radius fracture	1 (0.7%)	0	0	0	0	0	0	0	0	0
Spinal compression fracture	0	0	1 (0.7%)	0	1 (0.3%)	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0	1 (0.6%)	0	0	0	0
Hyperglycaemia	0	0	0	0	0	1 (0.6%)	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.7%)	0	0	0	0	0	0	0	1 (0.6%)	1 (0.3%)
Arthritis	0	0	0	0	0	0	0	0	1 (0.6%)	1 (0.3%)
Foot deformity	1 (0.7%)	0	0	0	0	0	0	0	0	0
Nervous system disorders	1 (0.7%)	0	0	0	0	0	0	1 (0.6%)	1 (0.6%)	2 (0.5%)
Cerebrovascular accident	0	0	0	0	0	0	0	1 (0.6%)	0	1 (0.3%)
Cerebrovascular insufficiency	1 (0.7%)	0	0	0	0	0	0	0	0	0
Syncope	0	0	0	0	0	0	0	0	1 (0.6%)	1 (0.3%)
Psychiatric disorders	1 (0.7%)	0	0	0	0	1 (0.6%)	1 (1.9%)	0	1 (0.6%)	2 (0.5%)
Anxiety	0	0	0	0	0	0	0	0	1 (0.6%)	1 (0.3%)
Depression	1 (0.7%)	0	0	0	0	1 (0.6%)	0	0	1 (0.6%)	1 (0.3%)
Suicidal ideation	1 (0.7%)	0	0	0	0	0	1 (1.9%)	0	0	1 (0.3%)
Renal and urinary disorders	0	0	1 (0.7%)	0	1 (0.3%)	0	0	0	1 (0.6%)	1 (0.3%)
Renal failure acute	0	0	1 (0.7%)	0	1 (0.3%)	0	0	0	0	0
Renal injury	0	0	0	0	0	0	0	0	1 (0.6%)	1 (0.3%)
Reproductive system and breast disorders	0	0	1 (0.7%)	0	1 (0.3%)	0	1 (1.9%)	0	0	1 (0.3%)
Benign prostatic hyperplasia	0	0	0	0	0	0	1 (1.9%)	0	0	1 (0.3%)
Cervical polyp	0	0	1 (0.7%)	0	1 (0.3%)	0	0	0	0	0

Attachment 19 Number of subjects with 1 or more treatment-emergent serious adverse events through Week 24 by MedDRA system-organ class and preferred term and by baseline MTX usage; treated subjects in PsA CNTO1275PSA3001 and CNTO1275PSA3002 studies

	Receiving MTX at Baseline Ustekinumab					Not Receiving MTX at Baseline Ustekinumab				
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined
Respiratory, thoracic and mediastinal disorders	1 (0.7%)	0	0	0	0	0	0	0	0	0
Interstitial lung disease	1 (0.7%)	0	0	0	0	0	0	0	0	0
Vascular disorders	1 (0.7%)	0	0	0	0	0	0	0	0	0
Hypertension	1 (0.7%)	0	0	0	0	0	0	0	0	0

[a] Subjects who early escaped at Week 16.
[b] Includes all subjects irrespective of early escape.

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In summary, the SAE data presented by SOC and PT term through Week 24 do not indicate that the nature of SAEs is different between subjects treated with concomitant MTX and those treated with ustekinumab monotherapy. SAEs were generally singular in nature and no patterns of SAEs were observed regardless of concomitant MTX use. The nature of the SAEs in those with or without concomitant MTX show no major differences and the numbers were limited.

Discontinuation due to adverse events

Through the placebo-controlled period (0-16 weeks) in the combined Phase 3 PsA studies, the overall incidence of treatment-emergent AEs leading to discontinuation of study agent was low. The proportion of subjects who discontinued study agent due to an AE was higher in the placebo group (3.6% [11 subjects]) compared with the combined ustekinumab group (1.1% [7 subjects]. The proportions of subjects who discontinued study agent due to an AE were similar in the 45 mg (1.0% [3 subjects]) and 90 mg (1.3% [4 subjects]) groups.

The SOCs with the highest proportions of discontinuations were Musculoskeletal and connective tissue disorders (2.3% [7 subjects] in the placebo group and 0.3% [2 subjects] in the combined ustekinumab group) and Skin and subcutaneous tissue disorders (0.6% [2 subjects] in the placebo group and 0.3% [2 subjects] in the combined ustekinumab group) most likely reflecting a lack of treatment benefit in the placebo group. Consistent with this, AEs leading to discontinuation of study agent of psoriatic arthropathy and psoriasis were highest in the placebo group followed by the 45 mg group and were absent in the 90 mg group (Other AEs leading to discontinuation of study agent generally occurred as single events without any notable patterns with regard to SOC or type of event and did not occur more

Through Week 52

Phase 3 CNTO1275PSA3001 PsA Study

Through Week 52 in the CNTO1275PSA3001 study in the 52-Week safety subset, AEs leading to discontinuation of study agent occurred in 2.0% (7 subjects) of subjects with available data in the combined ustekinumab group. The proportion of subjects with AEs leading to discontinuation of study agent was higher in the 45 mg group (3.3% [4 subjects]), compared with the 90 mg group (0.8% [1 subject]) although the overall incidence was low. Consistent with results through Week 24, the majority of AEs leading to discontinuation of study agent occurred as single events without any notable patterns with regard to SOC, type of event, or treatment group.

Adverse events of Special interest

Infections

Through the Placebo-controlled Period

PsA Compared with Ps

The proportions of subjects with infections were comparable across the placebo groups and all ustekinumab dose groups within the PsA and Ps studies, and the types of infections were generally comparable across all treatment groups without any clear dose response, with the exception of dental-related infections. Consistent with the analysis from the Phase 3 PsA studies, more dental-related infections (tooth infection and tooth abscess) occurred in ustekinumab-treated subject compared with placebo-treated subjects in the Phase 3 Ps studies, which supported the identification of dental infections as an ADR. The most frequently occurring types of infections (occurred in ≥2% of subjects in any treatment group) were similar between the PsA and Ps populations without any notable differences in the types of infections across treatment groups or between study populations. Infections that occurred in ≥2% of subjects in the combined ustekinumab group in both PsA and Ps were nasopharyngitis, upper respiratory tract infection, and sinusitis.

Through Week 24

PsA Compared with Ps

Through Week 24 in the Ps and PsA studies, the most frequently occurring types of infections in the combined ustekinumab group were nasopharyngitis, upper respiratory tract infection, sinusitis, gastroenteritis, and influenza. There were no clear dose responses observed between 45 mg and 90 mg groups in all the PsA and Ps studies.

Through Week 52

Phase 3 CNTO1275PSA3001 PsA Study

Through Week 52 in the CNTO1275PSA3001 52-Week safety subset, treatment-emergent infections occurred in 37.8% (131 subjects) of subjects with available data in the combined ustekinumab group.

The proportion of subjects with infections was similar in the 45 mg (42.5%) and 90 mg (42.4%) treatment groups. Consistent with results through Week 24, the most frequently occurring infections were nasopharyngitis and upper respiratory tract infections.

Serious infections

Through the end of the reporting period in the combined Phase 3 PsA studies, there was 1 serious infection in the placebo group (interstitial lung disease in the CNTO1275PSA3002 study), and 4 serious infections in the CNTO1275PSA3001 study in the combined ustekinumab group (cholecystitis in the placebo→45 mg group, acute cholecystitis and salpingitis in the 45 mg group and pharyngolaryngeal abscess in the 90 mg group).

Malignancies

Through the placebo-controlled period (0-16 weeks) in the combined Phase 3 PsA studies, there was 1 subject in the ustekinumab 90 mg group with squamous cell carcinoma in situ in an area of cleared plaque psoriasis.

Major Adverse Cardiovascular Events (MACE)

As in Ps, patients with PsA are reported to be at increased risk for occlusive vascular diseases, including MI and stroke. At least part of this increased risk results from higher rates of cardiovascular risk factors such as hypertension, hyperlipidaemia, diabetes, obesity, and smoking in the PsA population. While Ps patients with PsA appear to have higher rates of CV comorbidities compared with Ps patients without PsA, whether PsA is an independent CV risk factor still requires further study.

To evaluate the potential impact of ustekinumab on this population risk, the incidence of adjudicated MACE (cardiovascular death, nonfatal myocardial infarction, non-fatal stroke) were evaluated in the placebo-controlled period and through the end of the reporting period in the combined Phase 3 PsA studies.

Through the End of the Reporting Period

Through the end of the reporting period across indications, there were:

- 4 MACE in the PsA studies (1 nonfatal myocardial infarction in placebo, 1 nonfatal myocardial infarction and 1 nonfatal stroke in 45 mg, 1 nonfatal stroke in 90 mg),

- 41 MACE in the Ps studies (1 nonfatal myocardial infarction in placebo which occurred 3 days after Week 12 in a subject in the placebo group who never crossed over to receive ustekinumab; 3 cardiovascular deaths, 15 nonfatal myocardial infarctions, and 3 nonfatal strokes in the 45 mg group; and 3 cardiovascular deaths and 16 nonfatal myocardial infarctions in the 90 mg group), and

- no MACE in the Crohn's disease studies

In the PsA studies, the event rates of MACE per 100 subject-years in the placebo, 45 mg group, 90 mg group, and combined ustekinumab groups were 0.70, 0.78, 0.34, and 0.55, respectively. In the Ps studies, the event rates of MACE per 100 subject-years in the placebo, 45 mg group, 90 mg group, and combined ustekinumab groups were 0.55, 0.56, 0.36, and 0.44, respectively. When the rate of MACE was evaluated by the time period of exposure, (Years 1, 2, 3, 4, and 5), the event rates per 100 subject-years of follow-up showed no evidence of a dose response or an increase in event rates with increased exposure to ustekinumab. However, the interpretation is limited by the small number of events and the modest year-to-year variability.

Through the end of the reporting period in the PsA studies (C0743T10, CNTO1275PSA3001, and CNTO1275PSA3002), the SIR in the combined ustekinumab group was 1.24 (95% CI: 0.26, 3.63), and the SIR in the placebo group was 1.81 (95% CI: 0.05, 10.08); however, CIs were wide and overlapping.

Serious Neurologic Disorders

There were no events of RPLS reported in any PsA study with ustekinumab.

Injection-site Reactions

Through Week 24

Combined Phase 3 PsA Studies

Through Week 24, the number of injections associated with injection-site reactions was low in the combined Phase 3 PsA studies regardless of the study agent administered, although a modest increase was observed in injections of 90 mg, (0.4% of injections of placebo, 0.6% of injections of 45 mg, and 1.0% of injections of 90 mg). All injection-site reactions were mild, and none were moderate or severe or serious. The most common injection-site reactions through Week 24 were erythema and pain which are known ADRs.

PsA Compared with Ps

Through Week 24, there were similar average numbers of injections in each study agent group across the PsA and Ps populations. The proportion of injections associated with injection-site reactions was low across all study agent groups and comparable between the PsA studies and Ps studies. There were no moderate or severe injection-site reactions in the combined Phase 3 PsA studies, and 3 moderate and 1 severe injection-site reactions in the combined C0743T08 and C0743T09 Ps studies. The most common injection-site reactions through Week 24 in both the PsA and Ps populations were erythema and pain.

Through Week 52 in the CNTO1275PSA3001 52-Week safety subset, the proportion of injections associated with injection-site reactions was low and generally comparable across all groups (0.3% of injections of placebo, 0.5% of injections of 45 mg, and 0.6% of injections of 90 mg). All injection-site reactions were mild, and none were moderate or severe. The most common injection-site reaction through Week 52 was pain.

Post-marketing experience

Post-marketing information has been accruing since the first approval of ustekinumab on 12 Dec 2008. As of 30 Jun 2012, ustekinumab has subsequently been approved in over 65 countries. Global post-marketing exposure through 30 Jun 2012 has been estimated as 120,462 person-years. Biannual Periodic Safety Update reports (PSURs) have been generated for this product reflecting the assessment of active ongoing post-marketing surveillance of targeted safety events as described in clinical study safety analyses, as well as broad overall safety surveillance as described below.

Aggregate data from post-marketing reports are reviewed at defined intervals in conjunction with the preparation of the PSUR to monitor for changes in the overall AE pattern for ustekinumab over time, and for changes in the reporting frequency or severity of selected AEs in order to identify potential new safety concerns. In addition, trending and review of lot-related AEs or product quality/technical complaints with AEs from the global safety database are conducted at defined intervals to identify signals related to product quality and manufacturing. Finally, surveillance with trending of reported

event frequency over time, as well as comparison of event reporting disproportionality with other drugs from the Food and Drug Administration Adverse Event Reporting System (FDA AERS) and the World Health Organization (WHO) Vigibase databases is performed routinely.

Through 30 June 2012, 7 PSURs have been completed. Hypersensitivity reactions (including rash, urticaria) and serious allergic reactions, including anaphylaxis and angioedema occurring in conjunction with ustekinumab therapy were identified from spontaneous reports and were identified as ADRs. The safety concerns of serious infections, including TB and Salmonella, malignancies, MACE, RPLS, facial palsy, and pregnancy outcomes are under heightened surveillance. While the complete evaluation of NMSC has not suggested a causal relationship, a post-marketing case report was published in the Australasian Journal of Dermatology which described 2 patients older than 60 years of age, who developed multiple cutaneous SCCs after each receiving 2 doses of ustekinumab. Based on this information the sponsor has recently added a warning advising prescribers to monitor patients, in particular those greater than 60 years of age, those with a history of prolonged immunosuppressant therapy or those with a history of psoralen plus ultraviolet A light (PUVA) treatment, for the appearance of non-melanoma skin cancer. No additional ADRs have been identified from post-marketing reports through 30 Jun 2012.

2.5.2. Discussion on clinical safety

The MAH assessed safety and compared the relatively small safety database in PsA (213 patients for >12months) with the larger Ps safety database. In view of the similarity in patient demographics and baseline disease characteristics that supportive information from the ~9000 patient years of data for Ps is informative. As ustekinumab is licensed as monotherapy for Ps, the additional information from Crohn's disease is relevant although demographics differ markedly with those of Ps patients.

There were no new safety signals arising from the data, no evidence for a dose-effect and no evidence for a more severe adverse profile for those on concomitant MTX. New ADRs reported in the PsA studies were arthralgia, nausea and dental infection.

The absolute number of MACE events in the PsA studies are low but the event rates of MACE per 100 subject-years appears higher than in the Ps indication where there is over 9000 patients years of experience. In view of the small absolute numbers it is not possible to conclude on any difference for MACE incidence in PsA from the data through to the end of the reporting period. It is also not expected that there should be a different safety profile for patients treated for PsA as opposed to those treated for Ps as there is significant overlap in the manifestations of psoriasis and the background demographics and baseline risk factors for MACE are similar in those with skin and/or joint manifestations of psoriasis. Of note is that an additional 6 cases of MI (3 in each study) (5 recovered, for one case recovery was not reported) were reported after the 24week DBL and for 5 subjects the treatment was blinded. All subjects had at least 2 CV risk factors and half were on MTX. Monitoring of MACE events continues as part of the ongoing pharmacovigilance activities and further data on the safety profile of ustekinumab in PsA will become available from the two ongoing pivotal studies.

In terms of the assurance from the Ps safety data the main different for the PsA indication is the use of concomitant MTX. While supportive safety data from the Crohn's disease database was provided, as these patients were taking additional immunosuppressive medication, there remains the potential for a worse safety profile with ustekinumab is given with MTX in this patient population.

2.5.3. Conclusions on clinical safety

There were no new safety signals arising from the data, no evidence for a dose-effect and no evidence for a more severe adverse profile for those on concomitant MTX.

The RMP provided is considered appropriate for the PsA indication and the same risk minimisation activities than for Ps, which include a ustekinumab educational programme, are required. All safety concerns are appropriately reflected in the Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects sections of the Product Information.

Comparison of rates of important safety concerns subject to specific monitoring (serious infections, malignancies and MACE) events from clinical trials and external datasets in the psoriasis population does not suggest any excess risk associated with ustekinumab treatment. This is conclusion is supported by data from comparisons between the different patient cohorts in PSOLAR.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged and is currently yearly.

The annex II related to the PSUR, refers to the EURD list.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Important Identified Risks	– Serious systemic hypersensitivity – Facial palsy
Important Potential Risks	– Serious infections including mycobacterial and salmonella infections – Malignancy – Cardiovascular events – Serious depression including suicidality – RPLS – Exposure during pregnancy

Missing Information	– Use in paediatric patients – Use in patients with hepatic impairment – Use in patients with renal impairment – Use in patients with a history of latent TB or TB – Use in patients with concurrent malignancy or a history of malignancy – Use in patients with active infections (e.g. TB, HIV, hepatitis B, or hepatitis C) – Use after recent vaccination with live bacterial or live viral vaccines – Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy – Use in patients with other forms of PSO – Use in patients who have allergy immunotherapy

Pharmacovigilance plan

Summary of Outstanding Actions Including Milestones

Actions	Milestones/exposure	Milestones/calendar time	Study status
Submission of CNTO1275CRD3001 final data	675 subjects	Q4 2015	Ongoing
Submission of CNTO1275CRD3002 final data	600 subjects	Q4 2015	Ongoing
Submission of CNTO1275CRD3003 final data	1275 subjects	Q4 2015	Ongoing
Submission of CNTO1275PSO3006 final data	105 subjects	December 2014	Ongoing
Submission of CNTO1275PSA3001 final data	615 subjects	November 2013 (Interim data December 2012)	Ongoing
Submission of CNTO1275PSA3002 final data	312 subjects	June 2013 (Interim data December 2012)	Ongoing
Submission of 1275148SCD2001 final data	180 subjects	April 2013	Ongoing
Submission of CNTO1275PBC2001 final data	Phase 1: 20 subjects Phase 2: 108 subjects	TBD	Ongoing
Submission of CNTO1275ARA2001 data	250 subjects	TBD	Ongoing[a]
Submission of C0168Z03 (PSOLAR) data	4,000 subjects	December 2020 Next interim data January 2013	Ongoing
Submission of CNTO1275PSO4005 (Nordic Database Initiative) data	1,000 subjects	December 2020 Next interim data May 2013	Ongoing
Submission of CNTO1275PSO4007 (Pregnancy Research Initiative) data	200 subjects	December 2021 Next interim data May 2013	Ongoing

a: Study start date was 02 Jul 2012 (after 31 May 2012 cutoff) and is included here for completeness

Risk minimisation measures

Safety Concern	Risk Minimisation Measures (Routine and Additional)
Important Identified Risks	
Serious systemic hypersensitivity reactions	**Routine Risk Minimisation Activities:** Guidance is provided in the Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC. **Additional Risk Minimisation Activities:** Ustekinumab Educational Programme
Facial Palsy	**Routine Risk Minimisation Activities:** Guidance is provided in the Undesirable Effects section of the SmPC. **Additional Risk Minimisation Activities:** None
Important Potential Risks	
Serious infection including mycobacterial and salmonella infections	**Routine Risk Minimisation Activities:** Guidance is provided in the Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC. **Additional Risk Minimisation Activities:** Ustekinumab Educational Programme
Malignancy	**Routine Risk Minimisation Activities:** Guidance is provided in the Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC. **Additional Risk Minimisation Activities:** Ustekinumab Educational Programme
Cardiovascular events	**Routine Risk Minimisation Activities:** None **Additional Risk Minimisation Activities:** None
Serious depression including suicidiality	**Routine Risk Minimisation Activities:** Depression is listed in the Undesirable Effects section of the SmPC (Serious depression including suicidality is not specifically mentioned in the SmPC). **Additional Risk Minimisation Activities:** None.
RPLS	**Routine Risk Minimisation Activities:** None **Additional Risk Minimisation Activities:** None
Exposure during pregnancy	**Routine Risk Minimisation Activities**: Guidance is provided in the Fertility, Pregnancy and Lactation section of the SmPC. **Additional Risk Minimisation Activities:** None
Missing Information	
Use in paediatric patients	**Routine Risk Minimisation Activities:** The Posology and Method of Administration section in the SmPC indicates that safety in patients less than 18 years of age has not yet been established. **Additional Risk Minimisation Activities:** None
Use in patients with hepatic impairment Use in patients with renal	**Routine Risk Minimisation Activities:** Guidance is provided in the Posology and Method of Administration and the Pharmacokinetic Properties sections of the

impairment	SmPC. **Additional Risk Minimisation Activities:** None
Use in patients with a history of latent TB or TB Use in patients with concurrent malignancy or a history of malignancy Use in patients with active infections (e.g. TB, HIV, hepatitis B, or hepatitis C)	**Routine Risk Minimisation Activities:** Guidance is provided in the Special Warnings and Precautions for Use section of the SmPC. **Additional Risk Minimisation Activities**: None
Use after recent vaccination with live bacterial or live viral vaccines	**Routine Risk Minimisation Activities:** Guidance is provided in the Special Warnings and Precautions for Use and the Interaction with Other Medicinal Products and Other Forms of Interaction sections of the SmPC. **Additional Risk Minimisation Activities:** None
Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy	**Routine Risk Minimisation Activities:** Guidance is provided in the Special Warnings and Precautions for Use and Interaction with Other Medicinal Products and Other Forms of Interaction sections of the SmPC. **Additional Risk Minimisation Activities:** None
Use in patients with other forms of psoriasis	**Routine Risk Minimisation Activities:** None **Additional Risk Minimisation Activities:** None
Use in patients who have undergone allergy immunotherapy	**Routine Risk Minimisation Activities:** Guidance is provided in the Special Warnings and Precautions for Use section of the SmPC. **Additional Risk Minimisation Activities:** None

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The beneficial effects demonstrated in PsA with ustekinumab include improvement of rapid onset in joint disease, plaque psoriasis, health related quality of life, and in addition some improvement in dactylitis, spondylitis and enthesitis. The positive effects on all these outcomes were maintained at 12

weekly dosing up to week 24. The two pivotal trials were supportive of the proposed posology which is similar to that licensed in plaque psoriasis.

Uncertainty in the knowledge about the beneficial effects

Demonstration of long-term maintenance of effect remains to be provided from the ongoing main studies. Submission of these data is defined in the risk management plan.

The data on radiographic scores to support efficacy of ustekinumab in reducing the rate of progression of structural damage in PsA is not yet available. Radiographic data will be available from Phase 3 studies CNTO1275PSA3001 and CNTO1275PSA3002 and will be provided as defined in the RMP.

Risks

Unfavourable effects

The most common unfavourable effects of ustekinumab include infections, fatigue and injection site reactions. Other adverse events such as skin malignancies and MACE occur at a rate seen in the psoriasis population. Three new ADRs were identified in the PsA programme: arthralgia, nausea and dental infection. No new SAEs no opportunistic infections and no deaths were seen in the PsA programme.

Uncertainty in the knowledge about the unfavourable effects

As in Ps, patients with PsA are reported to be at increased risk for occlusive vascular diseases, including MI and stroke. However, in view of the small absolute numbers it is not possible to conclude on any difference for MACE incidence in PsA from the data through to the end of the reporting period. It is also not expected that there should be a different safety profile for patients treated for PsA as opposed to those treated for Ps as there is significant overlap in the manifestations of psoriasis and the background demographics and baseline risk factors for MACE are similar in those with skin and/or joint manifestations of psoriasis. Monitoring of MACE events continues as part of the ongoing pharmacovigilance activities as defined in the risk management plan.

There is >9000 patients years of safety data for ustekinumab monotherapy in plaque psoriasis. The longer term safety profile for add on therapy to MTX remains to be collected in PsA. Further data on the safety profile of ustekinumab in PsA will become available from the two ongoing from Phase 3 studies CNTO1275PSA3001 and CNTO1275PSA3002 studies.

Benefit-Risk Balance

The beneficial effects of ustekinumab in joint, skin, and in addition improvement in dactylitis, spondylitis and enthesitis skin and in quality of life endpoints are considered relevant. As there are limited treatments available for patients who have failed DMARDs for PsA, a treatment which has shown efficacy in multiple domains of the disease and in quality of life is a useful additional treatment option.

Importance of favourable and unfavourable effects

The favourable effect of rapid onset efficacy in those who have failed previous treatment for PsA is considered a very useful addition to therapies for PsA. Data on structural damage is not yet available

hence limiting the demonstrated benefit but this data is expected to be available in the future. This information will be established based on radiographic data collected from Phase 3 studies CNTO1275PSA3001 and CNTO1275PSA3002.

The unfavourable effects are described in the SmPC and no new SAEs no opportunistic infections and no deaths were seen in the PsA programme. No additional safety concerns are evidence at this stage for combined therapy with MTX. Longer term data will provide further information on this.

Overall at this stage the favourable effects outweigh the unfavourable ones, particularly as efficacy and safety in Ps are well established and there have been no post-marketing signals for any adverse effects on joint. In addition although the safety data base for Ps is limited to ~9000 patient years as compared with anti-TNFs, at this stage the safety profile of ustekinumab is considered favourable.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The beneficial effects of ustekinumab in joint, skin and in quality of life endpoints are considered relevant. As there are limited treatments available for patients who have previously failed DMARDs for PsA, a treatment which has shown efficacy in multiple domains of the disease and in quality of life is a useful additional treatment option.

The unfavourable effects of ustekinumab include infections, fatigue and injection site reactions. Other adverse events such as skin malignancies and MACE occur at a rate seen in the psoriasis population. Three new ADRs were identified in the PsA programme: arthralgia, nausea and dental infection. No new SAEs no opportunistic infections and no deaths were seen in the PsA programme.

The favourable effects outweigh the unfavourable effects. The B/R balance for ustekinumab in PsA is considered positive by the CHMP.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include the treatment of psoriatic arthritis for Stelara.

“STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).”

As a consequence, update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet has been updated accordingly.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing authorisation Holder (MAH) shall ensure that prior to launch of Stelara, all healthcare professionals who are expected to prescribe/use Stelara are provided with educational materials containing the following:

- Healthcare Professional educational pack
- Patient information pack

The key messages and components included in the Healthcare Professional educational pack are defined as follows:

- Summary of Product Characteristics
- Local Guidance for tuberculosis screening;
- Risk of serious infections, including salmonella, tuberculosis, and other mycobacterial infections;
- Risk of hypersensitivity reactions, including latex allergy;
- Risk of malignancies.

The key messages in the patient information pack are defined as follows:

- Patient Information Leaflet
- Risk of reactivation of latent tuberculosis and information about the screening for tuberculosis according to the local guidance;
- Risk of serious infections, including salmonella, tuberculosis, and other mycobacterial infections;
- Risk of hypersensitivity reactions, including latex allergy;
- Potential risk of malignancies;
- Appropriate techniques for self-administration of Stelara, including use of the prefilled syringes.