Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ustekinumab

Proprietary Product Name: Stelara

Sponsor: Janssen-Cilag Pty Ltd

First round CER: 25 June 2014

Second round CER: 26 September 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ADA	Anti-Drug Antibody
AE	Adverse Event
AS	Ankylosing Spondylitis
ANCOVA	Analysis of Covariance
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BLQ	Below Level of Quantification
BMI	Body Mass Index
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Confidence interval
CL/F	Apparent Clearance
CMH	Cochran-Mantel-Haenszel
CRP	C-Reactive Protein
CS	Corticosteroids
CV	Coefficient of Variation
DLQI	Dermatology Life Quality Index
DMARD	Disease Modifying Anti-Rheumatic Drug
ECLIA	Electrochemiluminescent Immunoassay
ES	Erosion Score
ESR	Erythrocyte Sedimentation Ratio
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
IL	Interleukin
JSN	Joint Space Narrowing

Abbreviation	Meaning
LEF	Leflunomide
LS	Least Square
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	Minimal Clinically Important Difference
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
PASI	Psoriasis Area Severity Index
PD	Pharmacodynamic
PhGADA	Physician Global Assessment of Disease Activity
PK	Pharmacokinetic
PsA	Psoriatic Arthritis
PT	Preferred Term
PtGADA	Patient Global Assessment of Disease Activity
PY	Patient-Years
QOL	Quality of Life
q12w	Every 12 weeks
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
SpA	Spondyloarthritis
SSZ	Sulfasalazine
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal
USK	Ustekinumab

Abbreviation	Meaning
vdH-S	van der Heijde-Sharp score (modified for PsA)
V/F	Apparent Volume of Distribution

1. Introduction

1.1. Submission type

This is a full submission to extend the indication for ustekinumab (USK) to include the treatment of psoriatic arthritis (PsA) in adult patients.

USK is currently approved for the treatment of moderate to severe plaque psoriasis in adult patients under the registered trade name of Stelara. The sponsor does not propose a different registered drug name for this indication. Furthermore, no change in the drug formulation or presentation is proposed.

1.2. Drug class and therapeutic indication

USK is a human IgG1 kappa monoclonal antibody that specifically binds to the shared p40 protein subunit of the human cytokines Interleukin (IL)-12 and IL-23. It has the ATC code L04AC05, which relates to immunosuppressant drugs in the subclass of Interleukin inhibitors. USK inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 binding to the IL-12 beta1 receptor protein expressed on the surface of immune cells. However, USK cannot bind to IL-12 or IL-23 that is already bound to IL-12 beta1 cell surface receptors.

The approved indication is:

> *Stelara is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.*

The proposed additional indication is:

> *Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms, including the inhibition of structural damage, of active psoriatic arthritis in adult patients (18 years or older).*

1.3. Dosage forms and strengths

The following dosage forms and strengths are currently registered: 45 mg of USK in 0.5 mL (presented in a single use vial or pre-filled syringe).

2. Clinical rationale

PsA is a chronic inflammatory arthritis associated with skin psoriasis which typically onsets between the ages of 30 and 55 years, and affects men and women equally. Skin psoriasis has prevalence in the general population of 2-3%, and it is estimated that approximately 30% of patients with skin psoriasis develop PsA (Mease 2011).

PsA is a multifaceted and heterogeneous disease, which affects the joints, soft tissues (enthesitis and dactylitis) and skin. All of the disease manifestations may affect functional capacity and QOL. There is also increased mortality with persistent, severely active PsA. Peripheral joint involvement with PsA may be polyarticular (35-40%) or oligoarticular (20-35%), and axial involvement (spondylitis) has been reported in 10-25% of patients. The PsA radiographic spectrum is highly variable and includes patients with mild, non-destructive disease to those with severe and debilitating deformities due to progressive joint disease. The diverse radiographic findings seen in PsA include erosions and joint space narrowing (JSN), soft tissue changes, and new bone formation.

USK neutralises the bioactivity of IL-12 and IL-23, which are pro-inflammatory cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12

stimulates natural killer cells and drives the differentiation of CD4+ T-cells toward the T-helper 1 (Th-1) phenotype and stimulates the production of interferon gamma (IFNγ). IL-23 induces the T-helper 17 (Th17) pathway and promotes the secretion of various other pro-inflammatory cytokines such as IL-17, IL-21 and IL-22. Both IL-12 and IL-23 are highly expressed in the synovium and entheses of patients with PsA, and patients with skin psoriasis over-express these cytokines in psoriatic plaques. In addition, mouse models of arthritis demonstrate that the injection of IL-23 has the capacity to provoke and maintain entheseal inflammation. Overall, by binding the shared p40 subunit of IL-12 and IL-23, USK appears to have robust biological plausibility in being able to treat both psoriasis and PsA through interruption of the TH1 and Th17 cytokine pathways, which are central to the pathology of the diseases (Schett et al, 2013).

Current approved treatment options in Australia for moderately to severely active PsA include NSAIDs; conventional non-biological DMARDs such as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF) and cyclosporine; as well as several anti-TNF drugs. Recent literature suggests that conventional DMARDs have modest efficacy in treating the signs and symptoms of PsA. In addition, while anti-TNF drugs have been shown to demonstrate significant efficacy in treating active PsA, a substantial proportion of patients are not achieving meaningful American College of Rheumatology (ACR) responses. Based on the current literature for anti-TNF therapies, ACR20 response rates range from 50-60% and ACR50 response rates are approximately 30-40%. As such, there is an unmet need for additional therapies for active, treatment refractory PsA. USK is a monoclonal antibody therapy that has a different mechanism of action to conventional DMARDs and anti-TNF drugs.

2.1. Guidance

This submission was consistent with the pre-submission planning advice given to the sponsor by the TGA. There is 1 specific regulatory guideline relevant to the requested indication in PsA. The TGA has adopted the EU guideline 'Guideline on Clinical Investigation for Medicinal Products for the Treatment of Psoriatic Arthritis' (effective 5 February 2008).

For the proposed extension of treatment indication to include active PsA, the sponsor has submitted 2 pivotal studies (PSUMMIT I and II), which is supported by a single Phase II trial (C0743T10). Both pivotal studies have provided reports at 24 and 52 weeks for efficacy assessment, and safety evaluations at 16, 24 and 52 weeks of treatment follow-up. One of the pivotal Phase III studies (PSUMMIT I) is ongoing but the long-term data (108 weeks of treatment follow-up) is not yet available for consideration at this stage. PsA is a chronic disease and therefore, symptomatic treatment is expected to be maintained in the long term. The regulatory guideline relating to the assessment of a drug treatment in PsA states that clinical efficacy can be demonstrated over 12-24 weeks of therapy in a controlled trial, but maintenance of treatment effect requires longer duration studies (for example, 1 year). The guideline also recommends for the provision of an adequate safety database that a minimum of 300 to 600 patients should be exposed to the proposed marketing dose for 6 months, and at least 100 patients be exposed for a minimum of 12 months.

In PsA subjects, there are 5 main domains to assess efficacy (each with recommended instruments):

1. Improvement of symptoms and signs of peripheral arthritis (for example, using ACR clinical criteria)
2. Improvement of physical function (for example, using HAQ)
3. Improvement of symptoms and physical function related to axial disease (for example, using BASDAI)
4. Slowing or prevention of structural damage (for example, using modified Sharp score), and
5. Prevention of disability.

This application in patients suffering PsA includes the additional component of inhibition of structural damage as measured by serial plain X-ray. In this submission, the sponsor has provided an integrated analysis report of the data collected in the 2 pivotal Phase III studies at 24 and 52 weeks of treatment, which assessed the rate of joint damage progression by plain X-ray. The relevant regulatory guideline regarding PsA states that radiographs should be taken at fixed and pre-defined time points, without specifying anything further about these time points. However, for comparative purposes the CPMP/EWP/556/95 (Rev 1) guideline on RA requires evidence of maintenance of radiographically demonstrated benefit out to 2 years, the first year of which must be blinded data acquisition. The PsA regulatory guideline also recommends that assessment of other important complementary domains such as skin disease activity, enthesitis, inflammatory markers (ESR or CRP), quality of life measures, and global disease assessments (by patients and/or physicians).

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- All 3 of the efficacy/safety studies contributed pharmacokinetic and pharmacodynamic data
- 1 population pharmacokinetic analysis
- 2 pivotal (Phase III) efficacy/safety studies – PSUMMIT I and PSUMMIT II
- No dose-finding studies
- 1 non-pivotal (Phase 2) efficacy/safety study – C0743T10
- Integrated analysis of radiographic data collected in the 2 pivotal Phase III studies.

The submission contains 2 pivotal Phase III controlled trials (PSUMMIT I and PSUMMIT II) for the requested extension of indication to include the treatment of PsA. The 2 pivotal studies were designed with similar schema, eligibility criteria, as well as doses and regimens of therapy, so that the potential effect of USK on structural damage (as assessed by serial radiographs) could be evaluated from a pooled analysis at 24 and 52 weeks of treatment follow-up. However, the 2 studies were designed to independently evaluate the effect of USK on PsA signs and symptoms, physical function and health related quality of life (QOL). For both pivotal studies, the 24-week study reports provided in this submission were intended to provide the principal efficacy data supporting the indication of treating the signs and symptoms of PsA. However, the 52-week report for the PSUMMIT I trial, and the data collected up to Week 60 in PSUMMIT II were intended to complement the dataset for evaluating clinical efficacy and safety.

The sponsor has also submitted a single, placebo controlled Phase II study (C0743T10) in adult patients with PsA as supportive evidence. In this trial, patients were randomised to receive either placebo or USK 90mg by subcutaneous injection at Weeks 0, 1, 2 and 3. At Week 12, subjects randomised to placebo were to receive USK 90mg at Weeks 12 and 16.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

All of the studies in the USK clinical development program for the treatment and prevention of PsA were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

All 3 of the PsA studies collected data for pharmacokinetic (PK) assessment in the target population.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies in humans. The following information is derived from the sponsor's summaries in Modules 1 and 2, as well as the currently approved product information.

USK is slowly absorbed from the site of SC injection, reaching maximum serum concentration 8.5 days after administration. Absolute bioavailability is approximately 57%, and the apparent volume of distribution at steady state in adult subjects with psoriasis is 57-83 mL/kg. The median half-life of USK in patients with PsA is 22.4 days, but with significant inter-individual variability (range: 15-32 days). The exact metabolic pathway for USK is unknown. The key PK variables observed in patients with psoriasis are consistent with those seen in healthy subjects. Serum USK concentrations are impacted by subject weight with patients weighing > 100 kg showing lower serum USK concentrations compared to those weighing < 100 kg. This observation has been observed in a population analysis using data from adult patients with psoriasis. The median clearance of USK in patients weighing > 100 kg is approximately 37% higher compared to with patients weighing < 100 kg. Similarly, subjects with diabetes mellitus have a higher clearance of USK (29% higher mean) than those without diabetes. No specific studies have been performed to assess the effect of renal or hepatic impairment, age or gender on the PK of USK. The PK of USK does not appear to be significantly affected by the concurrent use of MTX, NSAID or cyclosporine in adult patients with psoriasis.

4.2.1. Physicochemical characteristics of the active substance

USK is a genetically engineered, humanised monoclonal antibody which has an approximate molecular weight of 149 kD. The sponsor does not propose any change to the physiochemical structure or manufacturing process with this application for extension of indication.

4.2.2. Pharmacokinetics in the target population

In the two Phase III PsA studies, serum USK concentrations were measured in samples collected at baseline, as well as weeks 4, 12, 16, 20, 24, 28, 40 and 52. In the Phase II study, CO743T10, serum USK concentrations were measured in samples collected at baseline, weeks 1, 2, 3 and 4, and every 4 weeks thereafter through to Week 36 (except no sample was collected at Week 32). In all three PsA studies, when study medication was scheduled to be administered at a particular visit, the blood sample for PK analysis was taken immediately prior to treatment administration. In the two Phase III studies, a validated Electrochemiluminescent Immunoassay (ECLIA) method was used to determine serum USK concentrations. The BLQ (Below the Lowest Quantifiable) sample concentration of the assay was < 0.16880 µg/mL (derived by the Lower Limit of Quantification [LLOQ] multiplied by the minimum required dilution [MRD] of 1:10). A traditional non-compartmental analysis was used to estimate the PK parameters of USK in the Phase II study (C0743T10) with relatively intense serum sampling. However, a population PK

approach was used to analyse the Phase III PsA data and to determine the typical PK parameters of USK and the inner- and intra-individual variability of the PK USK in subjects with PsA. This approach is similar to what was used for the Phase III psoriasis studies (C0734T08 and C0743T09).

4.2.2.1. PSUMMIT I Study (also known as CNTO1275PSA3001)

A total of 615 subjects (53.7% male, 96.6% Caucasian) with a median body weight of 86.0 kg (range: 41 - 200 kg) and a median age of 48.0 years (range: 18 - 81 years) were randomised into this trial. Of these 615 subjects, 154 (25.0%) had a body weight > 100 kg at baseline, and 48.1% took concurrent MTX during the study. Specific details regarding the study design were provided.

Dose proportionality in serum USK concentration was observed when comparing mean serum USK concentrations between the 45 mg and 90 mg groups. Mean serum USK concentrations at Weeks 4, 12, 16, 20 and 24 in the 90 mg dose group were 1.9 to 2.0 fold higher than those at each respective sampling time point in the USK 45 mg dose arm – refer to Table 1. Serum USK concentrations exhibited a moderate to large inter-subject variability. Across dose groups and sampling time points, the percentage coefficient of variance (CV%) of serum USK concentrations ranged from 47.3% to 133.4%. There was no evidence of accumulation in serum USK concentrations over time. In both the 45 mg and 90 mg dose groups, mean serum USK concentrations at Week 24 (that is, 8 weeks after the third dose at Week 16) were slightly lower than those at Week 12 (that is, 8 weeks after the second dose at Week 4). At Week 16, 68 (34.5%) subjects in the USK 45 mg group and 32 (16.5%) subjects in the 90 mg group had trough BLQ serum USK concentrations. In the placebo early escape (placebo → 45 mg, n = 58) group, the mean serum USK concentration at Week 20 (that is, 4 weeks after the first 45 mg dose at Week 16) was comparable to that observed at Week 4 in subjects who were originally randomised to the 45 mg group (n = 169). At Week 16, the proportion of subjects with BLQ serum USK concentrations was higher in subjects in the early escape (45 mg → 90 mg) group (45.7%) than those in subjects who did not early escape and maintained 45 mg dosing (32.1%). This is consistent with the observation of lower serum USK concentrations in subjects who early escaped at Week 16.

Table 1: Serum USK Concentrations (mcg/mL) Through to Week 24 in the PSUMMIT Studies.

	CNTO1275PSA3001 Ustekinumab 45 mg Combined[a]	CNTO1275PSA3001 Ustekinumab 90 mg[b]	CNTO1275PSA3002 Ustekinumab 45 mg Combined[a]	CNTO1275PSA3002 Ustekinumab 90 mg[b]
Subjects treated with ustekinumab	205	204	103	104
Week 0				
N	203	200	101	104
Mean (SD)	0.00 (0.046)	0.03 (0.434)	0.00 (0.024)	0.00 (0.000)
Median	0.00	0.00	0.00	0.00
Week 4				
N	200	196	101	103
Mean (SD)	1.84 (1.046)	3.49 (1.794)	1.58 (1.028)	3.30 (1.886)
Median	1.71	3.39	1.43	3.43
Week 12				
N	195	192	97	98
Mean (SD)	1.13 (0.957)	2.17 (1.547)	0.91 (0.873)	2.12 (1.626)
Median	0.89	1.87	0.80	1.88
Week 16				
N	197	194	97	96
Mean (SD)	0.46 (0.493)	0.93 (0.856)	0.38 (0.539)	0.93 (0.857)
Median	0.33	0.73	0.23	0.86
Week 20				
N	157[c]	189	75[c]	92
Mean (SD)	2.36 (1.416)	4.69 (2.381)	1.85 (1.159)	4.08 (2.153)
Median	2.19	4.51	1.77	3.92
Week 24				
N	149[c]	181	76[c]	92
Mean (SD)	1.04 (0.823)	1.98 (1.377)	0.74 (0.621)	1.70 (1.166)
Median	0.89	1.68	0.64	1.51

[a]Includes all subjects who received 45 mg.
[b]Includes all subjects irrespective of early escape.
[c]Subjects who did not early escape at Week 16.

The impact of body weight on the PK of USK was examined by comparing serum USK concentrations between subjects weighing ≤ 100 kg at baseline and subjects with weight > 100 kg, within each dose group and across the 45 mg and 90 mg USK dose groups. Serum USK concentrations were affected by body weight. Within each dose group, mean serum USK concentrations in subjects with weight > 100 kg at baseline were lower than the concentrations observed at each respective sampling time point in subjects with weight ≤ 100 kg at baseline. In the combined 45 mg group, mean serum USK concentrations at Weeks 4, 12 and 16 in subjects weighing > 100 kg were 35-50% lower than those observed at each respective time point in subjects with weight ≤ 100 kg. In the USK 90 mg group, mean serum USK concentrations at Weeks 4, 12, 16, 20 and 24 in subjects with weight > 100 kg at baseline were 32-53% lower than those observed at each respective time point in subjects weighing ≤ 100 kg. When comparing serum USK concentrations across the 45 mg and 90 mg groups, mean serum USK concentrations at Weeks 4, 12, and 16 in subjects weighing > 100 kg in the 90 mg group were generally comparable to those observed at the respective time points in subjects ≤ 100 kg in the combined 45 mg group. Mean serum USK concentrations at Week 20 and 24 in subjects > 100 kg in the 90 mg group were also generally comparable to those observed at the respective time points in subjects ≤ 100 kg in the 45 mg group who did not early escape at Week 16 (that is, the USK 45 mg only group). Consistent with the observation of lower serum USK concentrations in subjects weighing > 100 kg, the proportions of subjects with BLQ serum USK concentrations at Week 16 were higher in subjects weighing > 100 kg than in subjects weighing ≤ 100 kg in both

the combined 45 mg and the 90 mg group. Just over 50% of subjects weighing > 100 kg in the combined 45 mg group had BLQ serum USK concentrations at Week 16. In contrast, the proportions of subjects with BLQ serum USK concentrations at Week 16 were comparable between subjects > 100 kg in the 90 mg and subjects ≤ 100 kg in the combined 45 mg group (28.0% and 29.1%, respectively).

In the combined 45 mg group, mean serum USK concentrations at Weeks 4, 12, and 16 in subjects who received MTX concomitantly were 22-39% higher than those observed at each respective time point in subjects who did not receive MTX. In the USK 90 mg dose group, mean serum USK concentrations at Weeks 4, 12, 16, 20 and 24 in subjects who received MTX concomitantly were 11 - 21% higher than those observed at each respective time point in subjects who did not receive MTX.

These results could be confounded by other factors as there were minor differences in subject weight in those receiving concurrent MTX (85.0 kg) versus subjects not receiving MTX (89.0 kg). In addition, the incidence of antibodies to USK through to Week 24 was lower in subjects who received MTX concomitantly (3.3%) compared with subjects who did not receive MTX (8.1%). A more comprehensive population PK analysis using all the available data from the Phase III PsA studies accounting for the effects of other variables did not show a clinically relevant effect of MTX on the apparent clearance of USK.

4.2.2.2. PSUMMIT II Study (also known as CNTO1275PSA3002)

A total of 312 subjects (52.6% female, 94.8% Caucasian) with a median body weight of 88.3 kg (range: 41 - 179 kg) and a median age of 49.0 years (range: 19 - 75 years) were randomised into this trial. Of these 312 subjects, 90 (28.9%) had body weight > 100 kg. At baseline, 49.7% of subjects were receiving MTX and maintained stable doses of MTX throughout the study; and 180 (57.7%) subjects had prior exposure to anti-TNF drugs. Of the subjects previously treated with anti-TNF, 41.7% received concurrent MTX during this trial, while 60.6% of anti-TNF naïve subjects received MTX.

In the PSUMMIT II Study, dose proportionality in serum USK concentration was observed when comparing mean serum USK concentrations between the USK 45 mg and 90 mg groups – refer to Table 1. Mean serum USK concentrations at Weeks 4, 12, and 16 in the 90 mg dose group were 2.1 to 2.4 fold higher than those at each respective sampling time point than in the combined USK 45 mg group. Mean serum USK concentrations at Weeks 20 and 24 in the 90 mg arm were also 2.2 to 2.3 fold higher than those at each respective sampling time point in the 45 mg group in subjects who did not early escape but maintained 45 mg dosing at Week 16. Serum USK concentrations exhibited a moderate to large inter-subject variability. Across dose groups and sampling time points, the CV% of serum USK concentrations ranged from 52.8% to 152.4%. There was no evidence of accumulation in serum USK concentrations over time. In both the 45 mg only (subjects who did not early escape but maintained 45 mg dosing at Week 16) and 90 mg groups, mean serum USK concentrations at Week 24 (that is, 8 weeks after the third dose at Week 16) were slightly lower than those at Week 12 (that is, 8 weeks after the second dose at Week 4).

At Week 16, 41 (42.3%) subjects in the combined USK 45 mg group and 21 (21.9%) subjects in the 90 mg group had BLQ trough serum USK concentrations. In the placebo early escape (placebo → 45 mg, n = 31) group, the mean serum USK concentration at Week 20 (that is, 4 weeks after first 45 mg injection at Week 16) was comparable to that observed at Week 4 in subjects who were originally randomised to the USK 45 mg dose group (n = 83).

Unlike the results of the PSUMMIT I trial, this study demonstrated that for subjects in the USK 45 mg group, mean serum USK concentrations at Weeks 4, 12, and 16 in subjects who early escaped at Week 16 (45 → 90 mg) appeared to be approximately 26-56% higher than those observed at each respective sampling time point in subjects who did not early escape and maintained 45 mg dosing at Week 16 (that is, 45 mg only group). Consistent with this

observation, at Week 16 the proportion of subjects with BLQ serum USK concentrations was slightly lower in subjects in the 45 mg → 90 mg group (36.8%) than in subjects who did not early escape and maintained 45 mg dosing (43.6%). However, the converse was observed for subjects in the 90 mg group who qualified for early escape at Week 16. Their mean serum USK concentrations at Week 16 were 8 - 16% lower than those observed at each respective sampling time point in subjects who did not qualify for early escape at Week 16. These results should be interpreted with caution because of the limited number of subjects in the 45 mg group (n = 20) who early escaped at Week 16, as well as the moderate to large inter-subject variability in serum USK concentrations (CV% = 52.8% to 152.4%). The serum USK concentrations of subjects in the 45 mg early escape (45 mg →90 mg) group increased after receiving their first 90 mg dose at Week 16. At Week 24, mean serum USK concentrations were 0.74 µg/mL, 1.72 µg/mL and 1.70 µg/mL for the 45 mg only, 45 mg →90 mg, and 90 mg dose groups, respectively.

In the combined 45 mg group, mean serum USK concentrations at Weeks 4, 12, and 16 in subjects weighing > 100 kg were 28-51% lower than those observed at each respective time point in subjects weighing ≤ 100 kg. In the 90 mg dose group, mean serum USK concentrations at Weeks 4, 12, 16, 20, and 24 in subjects weighing > 100 kg were 33 - 64% lower than those observed at each respective time point in subjects weighing ≤ 100 kg. When comparing serum USK concentrations across the 45 mg and 90 mg groups mean serum USK concentrations at Weeks 4, 12, and 16 in subjects > 100 kg in the 90 mg group were generally comparable to those observed at the respective time points in subjects ≤ 100 kg in the combined 45 mg group. Mean serum USK concentrations at Weeks 20 and 24 in subjects > 100 kg in the 90 mg group were also generally comparable to those observed at the respective time points in subjects ≤ 100 kg in the 45 mg group who did not early escape at Week 16 (that is, the 45 mg only group). Consistent with the observation of lower serum USK concentrations in subjects weighing > 100 kg, the proportion of subjects with BLQ serum USK concentrations at Week 16 was higher in subjects weighing > 100 kg in the USK combined 45 mg and 90 mg groups (58.6% and 44.8%, respectively) compared with subjects weighing ≤ 100 kg (35.3% and 11.9%, respectively).

Unlike the results seen in the PSUMMIT I Study, no consistent trend in serum USK concentrations was observed between subjects who received MTX concomitantly and subjects who did not receive MTX in the PSUMMIT II Study. In the 45 mg only group, mean serum USK concentrations in subjects who received MTX concomitantly were generally comparable with those observed at Weeks 4, 12, 16, 20 and 24 in subjects who did not receive MTX (that is, they varied from approximately 28% lower to 27% higher). In the 90 mg group, mean serum USK concentrations at Weeks 4, 12, 16, 20, and 24 in subjects who received MTX concomitantly were generally similar or slightly higher than those observed in subjects who did not receive MTX (that is, varying from approximately 1% lower to 40% higher). In the 45 mg early escape (45 mg → 90 mg) group, mean serum USK concentrations at Weeks 4, 12, 16, 20, and 24 in subjects who received MTX concomitantly were 4 - 30% higher than those observed in subjects who did not receive MTX. In the placebo early escape (placebo → 45 mg) group, mean serum USK concentrations at Weeks 20 and 24 in subjects who received MTX concomitantly were 24-27% higher than those observed in subjects who did not receive MTX.

Among USK-treated subjects (n = 238), 137 (57.6%) subjects had prior biologic exposure to anti-TNF and 101 (42.4%) were anti-TNF naïve. Mean serum USK concentrations appeared to be generally lower in subjects who were previously treated with anti-TNF drugs when compared with those in subjects who were naïve. For example, in the combined USK 45 mg group, mean serum USK concentrations at Weeks 4, 12, and 16 in subjects who were previously treated with anti-TNF drugs were 25 - 49% lower than those observed at each respective time point in subjects who were naïve. In the USK 90 mg group, mean serum USK concentrations at Weeks 4, 12, 16, 20, and 24 in subjects who were previously treated with anti-TNF drugs were 18 - 34% lower than those observed at each respective time point in subjects who were anti-TNF naïve. However, subjects who were previously treated with anti-TNF had a higher mean body weight at baseline compared with subjects who were naïve (93.4 kg versus 86.2 kg.

Furthermore, the incidence of anti-USK antibodies through to Week 24 was also higher in subjects who were previously treated with anti-TNF (8.5% [n = 11]) compared with subjects who were naïve (3.1% [n = 3]). In addition, the moderate to large inter-subject variability in serum USK concentrations precludes a definite conclusion regarding the impact of previous anti-TNF experience on the PK of USK.

4.2.2.3. Study C0743T10

This was a Phase II, placebo-controlled study of USK 90 mg in subjects with active PsA. A total of 146 subjects (56.2% male, 94.5% Caucasian) with a median body weight of 90.9 kg (range: 55 - 143 kg) and a median age of 49.0 years (range: 23 - 74 years) were randomised into this trial. In this study, 20.5% of subjects were taking concomitant MTX, and 22.6% had prior experience with anti-TNF agents. A protocol amendment implemented after the commencement of subject recruitment changed the dosing of subjects from 90 mg per dose to approximately 63 mg per dose due to the implementation of a 0.22 µm filtration procedure used during study dose preparation which decreased the volume of drug that was able to be administered. A total of 36 subjects were randomised (17 to USK, and 19 to placebo) prior to implementation of this procedure.

At each weekly sampling time-point between weeks 1 and 4, serum USK concentrations were higher in subjects who received 90 mg x 4 injections than in subjects who received 63 mg x 4 injections, with the difference between the 2 dosages showing dose-proportionality. Concurrent MTX use or past exposure to biologic drugs showed no impact on serum USK concentrations, however, interpretation is limited by the small number of subjects meeting those characteristics.

4.2.3. Population pharmacokinetic analysis

For this submission, a confirmatory population PK analysis approach was used to evaluate the population PK of USK in subjects with active PsA using data from the 2 Phase III studies. A population PK model of USK using data collected from the Phase III psoriasis studies (C0743T08 and C0743T09) was used to help pre-specify the PsA population PK analysis model.

Based on the previous population PK model developed in adult subjects with psoriasis, a one-compartment PK model with first-order absorption and first-order elimination was selected as the structural PK model to fit the observed concentration data of USK following SC injections in subjects with PsA. Covariates to be evaluated in the analysis were pre-specified based on their likely pharmacological/physiological relevance and sample size. The standard model diagnostics demonstrated that the structural PK model used for the confirmatory population PK analysis was adequate in describing the concentration-time profiles of USK subjects with PsA.

A total of 2837 serum samples with quantifiable USK concentrations (1910 serum samples with quantifiable USK concentrations from 461 subjects in the PSUMMIT I Study, and 927 serum samples with quantifiable USK concentrations from 235 subjects in the PSUMMIT II Study) were collected at 5 scheduled post-baseline time points and were included in the population PK analysis.

The population estimates for apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.334 L/day and 9.43 L, respectively, for a PsA subject with a body weight of 90 kg. The inter-individual variability for the CL/F was estimated to be 34.3%. The effects of subject weight, age, sex, race, baseline creatinine clearance, baseline serum albumin, baseline PsA disease characteristics (PASI, DAS28, and duration of PsA), co-morbidity of diabetes, immunogenicity (status of antibodies to USK), concomitant medications (MTX, NSAID, or oral CS), and prior exposure to anti-TNF drugs were evaluated in pre-specified model to determine if they contributed to variability in the PK of USK in subjects with PsA. The ratio of CL/F or V/F between the 25th and 75th percentiles of a continuous variable or between 2 categories of a discrete variable along with the 90% confidence interval (CI) of the ratio was calculated. The

range of (0.80, 1.25) commonly used for bioequivalence analyses was used as one of the criteria for assessing clinical relevance.

Among all factors evaluated, only the effect of subject weight on the CL/F and V/F and the effect of the presence of anti-drug antibodies to USK on the CL/F were considered to be potentially clinically relevant in subjects with PsA. None of the other factors evaluated, including co-morbidity of diabetes, concomitant medications (MTX, NSAID, or oral CS) and prior exposure to anti-TNF drugs, appeared to have impacts on the CL/F of USK in subjects with PsA – refer to Table 2.

Table 2: Ratios (90% CI) of Covariate Effects for the Primary Analysis Model in the PSUMMIT Studies

Parameter/Variable	Ratio of Median Parameter Estimate	90% CI
V/F (L)	-	-
Weight	1.25	(1.22, 1.29)
CL/F (L/day)	-	-
Weight	1.32	(1.28, 1.37)
Immune Response Positive	1.55	(1.37, 1.73)
Status of diabetes	1.12	(1.04, 1.20)
Age	0.97	(0.95, 1.00)
Sex (female effect)	1.03	(0.98, 1.08)
Baseline PASI score	1.04	(1.01, 1.09)
Baseline DAS28 using CRP	1.06	(1.04, 1.09)
Disease Duration	1.04	(1.00, 1.08)
Nonsteroidal anti-inflammatory drugs	1.00	(0.95, 1.05)
Oral corticosteroids	1.04	(0.97, 1.11)
Albumin	0.93	(0.90, 0.96)
Methotrexate use	0.92	(0.88, 0.96)
Prior exposure to anti-TNFα agents	1.06	(1.00, 1.12)

The mean body weight of subjects included in the population PK analysis was 89.4 kg and the range was from 41 to 200 kg. The change in CL/F due to body weight was -16% to + 11% of the median CL/F estimate when body weight increased from the 25th percentile (75.0 kg) to the 75th percentile (101.5 kg) of the subject values. The ratio of median CL/F values in subjects with the 75th percentile versus subjects with 25th percentile of weight values was 1.32 and the 90% CI of the ratio was (1.28, 1.37). The change in V/F due to body weight was from - 13% to + 9% of the median V/F estimate when body weight increased from the 25th percentile to the 75th percentile of subject values. The ratio of the median V/F values in subjects with the 75th percentile versus subjects with 25th percentile of the weight values was 1.25 and the 90% CI of the ratio was (1.22, 1.29). These represent approximately 32% higher median CL/F value and 25% higher median V/F value in subjects with the 75th percentile of subject weight when compared with subjects with the 25th percentile of subject weight. Median CL/F and V/F values were 0.29 L/day and 8.6 L, respectively, in subjects ≤ 100 kg; and were 0.46 L/day and 11.2 L, respectively, in subjects > 100 kg. This represents approximately 59% higher CL/F and 30% higher V/F value in subjects with body weight > 100 kg compared to the respective values in subjects with body weight ≤ 100 kg.

Monte Carlo simulation was conducted and the model-predicted median serum USK concentration versus time profiles in subjects ≤ 100 kg and > 100 kg following SC administrations of 45 or 90 mg USK at Weeks 0, 4 and 16. The results suggest that subjects in

the 2 weight categories (≤ 100 kg or > 100 kg) could achieve comparable systemic exposure and nearly identical trough serum USK concentrations if subjects ≤ 100 kg were treated with the 45 mg dosing regimen and subjects > 100 kg were treated with the 90 mg dosing regimen.

A total of 40 (5.7%) subjects in the PSUMMIT studies tested positive for antibodies to USK and were included in the population PK analysis. The ratio of the median CL/F values in subjects positive for antibodies to USK versus subjects negative for antibodies to USK was 1.55 and the 90% CI of the ratio was (1.37, 1.73), which represents 55% higher median CL/F value in subjects who were positive for antibodies to USK when compared with subjects negative for antibodies to USK.

4.2.4. Exposure-response relationship

Data from the 2 Phase III studies was pooled to explore the relationship between serum USK concentration and efficacy. Clinical responses were evaluated in subjects with BLQ serum USK concentrations (< 0.16880 µg/mL; n = 162 subjects) and in subjects with quantifiable serum USK concentrations split into 2 groups of equal numbers (between 0.16880 to < 0.71155 µg/mL and ≥ 0.71155 µg/mL; n = 211 and 212 subjects, respectively). The ACR20 response rate at 24 weeks increased with increasing serum USK levels with the lowest responses seen in the BLQ group (38.9%) compared with the middle cohort (44.5%) and highest serum USK group (55.2%). The proportion of ACR50 responses followed the same pattern: 17.3% in the BLQ group, 25.1% in the middle cohort and 30.7% in the highest serum group. PASI 75 responses at Week 24 revealed a similar finding being significantly lower in the BLQ group (42.5%) compared with the 2 other serum USK cohorts (63.5% for the middle group and 66.2% for the highest serum USK group).

4.3. Evaluator's overall conclusions on pharmacokinetics

The sponsor has provided new PK data (trough USK concentrations collected every 1 - 4 weeks over 36 - 52 weeks of treatment) in this submission for adult patients with active PsA. The sponsor is proposing minor changes to the PK section of the current PI to include the new PK data.

The key PK findings for CZP use in patients with active PsA are:

- Dose proportionality in serum USK concentration was observed when comparing mean serum USK concentrations between the 45 mg and 90 mg groups.
- There was no evidence of accumulation in serum USK concentrations over time.
- A higher proportion of subjects with BLQ trough serum USK concentrations were observed in the 45 mg dose group compared with the 90 mg group.
- Within each dose group, subjects weighing > 100 kg had lower mean serum USK concentrations compared with subjects weighing ≤ 100 kg. When compared across 45 mg and 90 mg groups, mean serum USK concentrations in subjects > 100 kg in the 90 mg group were comparable to those observed in subjects ≤ 100 kg receiving 45 mg injections. Both Phase III studies and the population PK analysis confirmed this observation. These findings support the proposed dosing of USK 90 mg injections in subjects weighing > 100 kg.
- Within each dose group of the PSUMMIT I Study, mean serum USK concentrations in subjects who received MTX concomitantly were moderately higher compared with those in subjects who did not receive MTX but the other 2 studies and the population PK analysis did not support this observation.
- In the PSUMMIT II Study, subjects previously exposed to anti-TNF drugs had generally lower serum USK levels, which have may have been confounded by other variables such as a higher mean body weight and a higher incidence of anti-USK antibodies.

- Subjects who developed anti-USK antibodies had significantly lower trough USK concentrations as a result of increased plasma clearance of USK.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

In this submission, a limited amount of pharmacodynamic (PD) data was collected in the PSUMMIT I and C0743T10 studies. In particular, the effects of USK on serum biomarkers of interest were assessed in both studies, and the PSUMMIT I Study also examined the potential effect of USK on various types of T-lymphocytes.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans. The following information is derived from the sponsor's summaries in Modules 1 and 2, as well as the currently approved product information.

5.2.1. Mechanism of action

USK is a human IgG1 kappa monoclonal antibody that specifically binds to the shared p40 protein subunit of the human cytokines IL-12 and IL-23. USK inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 binding to the IL-12 beta1 receptor protein expressed on the surface of immune cells. However, USK cannot bind to IL-12 or IL-23 that is already bound to IL-12 beta1 cell surface receptors. As such, USK is not expected to contribute to complement or antibody mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors.

IL-12 and IL-23 are pro-inflammatory cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 stimulates natural killer cells and drives the differentiation of CD4+ T-cells toward the T-helper 1 (Th-1) phenotype and stimulates the production of interferon gamma (IFNγ). IL-23 induces the T-helper 17 (Th17) pathway and promotes the secretion of various other pro-inflammatory cytokines such as IL-17, IL-21 and IL-22. Both IL-12 and IL-23 are highly expressed in the synovium and entheses of patients with PsA, and patients with skin psoriasis over-express these cytokines in psoriatic plaques. In addition, there is evidence that IL-23 has an effect bone erosion and destruction through up-regulation of receptor activator of nuclear factor kappa-β ligand (RANKL), which activates osteoclasts.

5.2.2. Pharmacodynamic effects

5.2.2.1. Effect on serum biomarkers

Serum biomarker samples from the PSUMMIT I Study were analysed for proteins shown to be associated with PsA or RA, and/or the IL-12/23 pathway. Proteins included markers of systemic inflammation and disease progression such as the S100 calcium binding protein A8 (S100A8), S100 calcium binding protein A9 (S100A9), Vascular Endothelial Growth Factor (VEGF), IL-6, IL-8, macrophage colony-stimulating factor 1 (MCSF-1), melanoma inhibitory activity, chitinase-3-like protein 1 (YKL-40), macrophage chemo attractant protein 1 (MCP-1), macrophage derived chemokine (MDC) as well as bone/cartilage metabolism markers such as osteoprotegerin and RANKL. The analyses were performed to assess whether these proteins were dysregulated in PsA subjects, were associated with the subtype severity of disease or change in severity (assessed by ACR50 and PASI 75 response), were affected by USK (anti-IL-12) administration, or were associated with response to treatment (measured by improvement in ACR and PASI at Week 24).

To assess the dysregulation of the serum proteins in PsA, the baseline (Week 0) protein concentrations in PsA subjects were compared to normal healthy donor protein concentrations. Six of the 12 proteins measured were dysregulated in PsA serum with S100A8, IL-6, MCP-1, YKL-40 and S100A9 ($p < 0.05$, Fold Change (FC) > 1.2) significantly elevated, and MCSF-1 significantly lower in PsA compared to healthy normal controls. All but 2 of the analytes were expressed, as determined by standard immunoassay, by all subjects with PsA. However, serum IL-6 was only detected in 58.9% of subjects and VEGF in 77.7% of subjects.

Measures of disease severity (such as the ACR, DAS28 and PASI criteria) as well as prior MTX use were assessed against protein levels at baseline. There were no significant differences in baseline protein levels by dose group, clinical subtype of PsA (for example, mainly affected by dactylitis at baseline) and prior MTX use. No single analyte showed a significant correlation with DAS28 score. However, 6 of the analytes measured had significant correlations with CRP levels (S100A8, IL-6, IL-8, S100A9, MCSF-1 and YKL40; correlation coefficients ranging from $r = 0.12$ to $r = 0.43$). Of these analytes, IL-6 showed the strongest correlation to CRP. CRP is known to be a downstream mediator of the IL-6 signalling pathway. The analytes showed no correlation to PASI, BASDAI or dactylitis scores at baseline or Week 24. MCSF-1 showed a weak but significant correlation to the enthesitis score at both baseline and Week 24.

The percent change from baseline in each analyte for each USK dose group in the PSUMMIT I Study was calculated at Week 4 and 24 to improve understanding of treatment effects. VEGF and MCSF-1 levels showed a small decrease at Week 4 indicating possible early response, which was not apparent at Week 24. YKL-40 was significantly decreased in the USK-treated groups as compared to placebo only at Week 24 (but not at Week 4) suggesting that the effect of the treatment on this serum marker requires a longer duration of treatment than the early response markers.

The association between clinical response and serum protein level change was assessed overall and by each treatment group. The effects of USK were assessed by comparing pre- versus post-treatment levels of a protein for joint and/or skin responders, and non-responders in each dose group. A high level of joint response was classified as ACR50 response at Week 24. Skin response was defined as a PASI 75 response at Week 24. To better characterize subjects who responded to treatment at Week 24 (responders) versus subjects who showed no response, differences in protein levels at baseline, Week 4, and Week 24 were compared to determine if a change in baseline level of a protein was associated with clinical response through to Week 24. Subjects in the USK 90 mg group who achieved an ACR50 response at Week 24 had decreased baseline levels of MCSF-1 as compared to non-responders, and this decrease was also observed when the 2 USK dose groups were combined. There were no significant differences between PASI 75 responders versus non-responders at baseline. No significant trends were observed in analyte levels for ACR50 or PASI 75 responders at Week 4 or Week 24 compared to non-responders.

In the Phase II Study C0743T10, 4 serum biomarkers thought to be associated with active PsA were investigated: VEGF, soluble IL-2 receptor, osteocalcin and matrix metalloproteinase 3. At baseline, mean serum levels for all 4 biomarkers were not significantly elevated compared to those reported in the literature for healthy adults. Minimal changes (< 10% mean change) from baseline were observed at 12 weeks with no trend for change following USK treatment being observed.

5.2.2.2. Effect on lymphocytes

It has been reported that there is a decrease in the number of natural killer (NK) T-cells in subjects lacking a functional IL-12/23 pathway. The effect of USK treatment on circulating immune cells, including T-cells, T helper cells, cytotoxic T cells, NK cells, NK-like T cells, and B cells, was analysed at Week 24 in the PSUMMIT I Study. The results demonstrate minimal changes (< 5% change) from baseline to 24 weeks in the mean or median percentage in the

number of lymphocytes assessed. No depletion nor expansion of T-cells or other immune cells (B or NK cells) were observed following treatment with USK.

5.2.3. Time course of pharmacodynamic effects

The clinical outcome data (ACR and PASI response) appears to indicate that USK has an onset of clinical effect as early as 4 weeks after initiation, which peaks at 24 - 28 weeks after commencement of therapy and then persists for up to 12 weeks after the last dose is administered. The serum biomarker data indicates that USK has an onset of PD effect from 4 weeks after first drug administration.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

The studies did not specifically examine the relationship between USK concentration and PD effects. However, information regarding the relationship between drug concentration and clinical response has already been discussed above.

5.3. Evaluator's overall conclusions on pharmacodynamics

The serum biomarker data from the PSUMMIT I Study indicates that PsA produces systemic inflammation that is measurable in the serum. However this observation was not supported by the Phase II trial (C0743T10) and no strong associations were observed between any serum biomarkers and baseline disease severity, or joint and/or skin response. A wide range of expression levels were observed for several of the analytes in the PsA population as a whole, and this heterogeneity may contribute to the lack of significance of a marker when assessed at the level of the population rather than by individual response. Two analytes showed weak but significant correlation to the severity of joint disease (IL-6 and MCSF-1 correlated with DAS28 response) but there was no correlation seen with any analyte and the severity of skin disease (PASI 75). Inflammation markers such as VEGF, MCSF-1 and YKL-40 showed modest differences in serum concentration primarily at Week 4 when USK-treated subjects were compared to placebo-treated subjects. These decreases may be related to the PD effects of USK in subjects with PsA. Furthermore, USK does not appear to have an effect on circulating immune cells (that is, various types of T- and B-lymphocytes).

6. Dosage selection for the pivotal studies

The USK dose examined in both PSUMMIT studies was justified from the results of the 2 pivotal Phase III trials of USK in subjects with psoriasis (Studies CO743T08 and C0743T09) and the Phase II C0743T10 Study in subjects with PsA (as part of this submission).

Studies C0743T08 and C0743T09 evaluated the efficacy and safety of 2 dosing regimens for USK in the treatment of moderate to severe plaque psoriasis: 45 mg at given weeks 0 and 4, followed by q12w dosing thereafter, and 90 mg administered at Weeks 0 and 4, and subsequently q12w. Both USK dosing regimens led to a statistically significant, rapid onset of efficacy in adult patients with skin psoriasis. Higher proportions of subjects (66.4% - 75.7% across the USK treatment groups in each study) compared with subjects in the placebo group (3.1% to 3.7%) achieved a PASI 75 response at Week 12 (the primary endpoint of both pivotal trials in psoriasis). Furthermore, with maintenance dosing of q12w in both studies, PASI response rates continued to improve up until Week 28 of follow-up, with consistent treatment related results observed across both studies. In contrast to the 2 psoriasis trials, Study C0743T10 did not evaluate a USK maintenance dosing regimen. In this Phase II trial, patients were randomly assigned to 1 of 2 treatment groups. The first group (n = 76) received 4 weekly injections of USK 90 mg at Weeks 0, 1, 2 and 3. The second group (n = 70) received matching placebo injections at Weeks 0, 1, 2 and 3; and then crossed over to receive USK at Weeks 12 and 16. The primary efficacy endpoint was assessed at 12 weeks but subjects were followed through to 36 weeks

post-baseline. Despite the design, Study C0743T10 appeared to show that USK had a maintenance of effect (as reflected by the rate of ACR20 and ACR50 response and PASI response) for at least 12 weeks following the last dose of USK administered whether it was following the initial 4 weekly doses of USK 90 mg, or the 2 doses of USK 90 mg given 4 weeks apart in placebo subjects who crossed over to USK at Week 12. Eventually, however, it did appear that USK had a waning effect within 16 to 20 weeks of last dose administered in a small number of subjects, indicating, as with all biologic agents for the treatment of PsA, that maintenance dosing would be indicated. In addition, a greater waning of USK effect was noted in the proportion of PASI 75 responders 12 to 16 weeks after their last dose of USK. Unlike Studies C0743T08 and C0743T09, the 45 mg dose of USK was not examined in Study C0743T10. During the course of Study C0743T10, Centocor (the drug manufacturer) added a filtration procedure during dose preparation for safety reasons. As a result of the filtration process, the volume of USK after filtration was reduced from 1.0 mL to 0.70 mL (hence, the USK dose was reduced from 90 mg to 63 mg per injection). The first 36 patients in the study (17 in the USK arm) were randomised prior to the filtration procedure being implemented and received USK 90 mg x 4 injections (360 mg in total). USK treated subjects randomised after the filtration process was commenced (n = 59), received USK 63 mg x 4 injections (252 mg in total), and crossover patients had their Week 12 and 16 doses of USK reduced from 90 mg x 2 to 63 mg x 2 (n = 57 at Week 12 and n = 55 at Week 16). Despite the small patient numbers, there was little difference in the rate of ACR20 response after 12 weeks of exposure in subjects who received doses of USK between 126 mg (2 x 63 mg doses) and 360 mg (4 x 90 mg doses), and therefore the sponsor concluded that an induction regimen of USK 90 mg to 180 mg (based on 2 doses of 45 mg or 90 mg) seemed reasonable for examination in the Phase III PsA study program.

In summary, the combined results of Studies C0743T08, C0742T09 and C0743T10 suggested that the USK dose regimen of either 45 mg or 90 mg at Weeks 0 and 4, followed by q12w administration of USK thereafter as maintenance therapy was appropriate to further evaluate the induction and maintenance of both skin and joint responses in adult patients with active PsA. Hence, both of these USK dose regimens were investigated in the 2 pivotal Phase III Studies in PsA (PSUMMIT I and II). In addition, the incidence and doses of background treatment with conventional DMARDs (mainly, MTX), CS and NSAID when used by patients in the pivotal studies were appropriate, and consistent with contemporary clinical practice in Australia.

7. Clinical efficacy

7.1. Indication 1:

'Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms, including the inhibition of structural damage, of active psoriatic arthritis in adult patients (18 years or older).'

7.1.1. Pivotal efficacy studies

7.1.1.1. Study CNTO1275PSA3001 (PSUMMIT I Study)

7.1.1.1.1. Study design, objectives, locations and dates

The PSUMMIT I trial was a Phase III , randomised, double-blind, placebo-controlled study evaluating the effect of USK in adult subjects with active PsA for at least 6 months despite previous or current treatment with NSAID and/or DMARD, and were naïve to anti-TNF therapy. NSAID treatment was defined as taking a NSAID for at least 4 weeks, and DMARD therapy was defined as taking such treatment for at least 3 months (or documented evidence of DMARD intolerance). MTX use at a dose ≤ 25 mg/week was allowed during the study but was not mandatory.

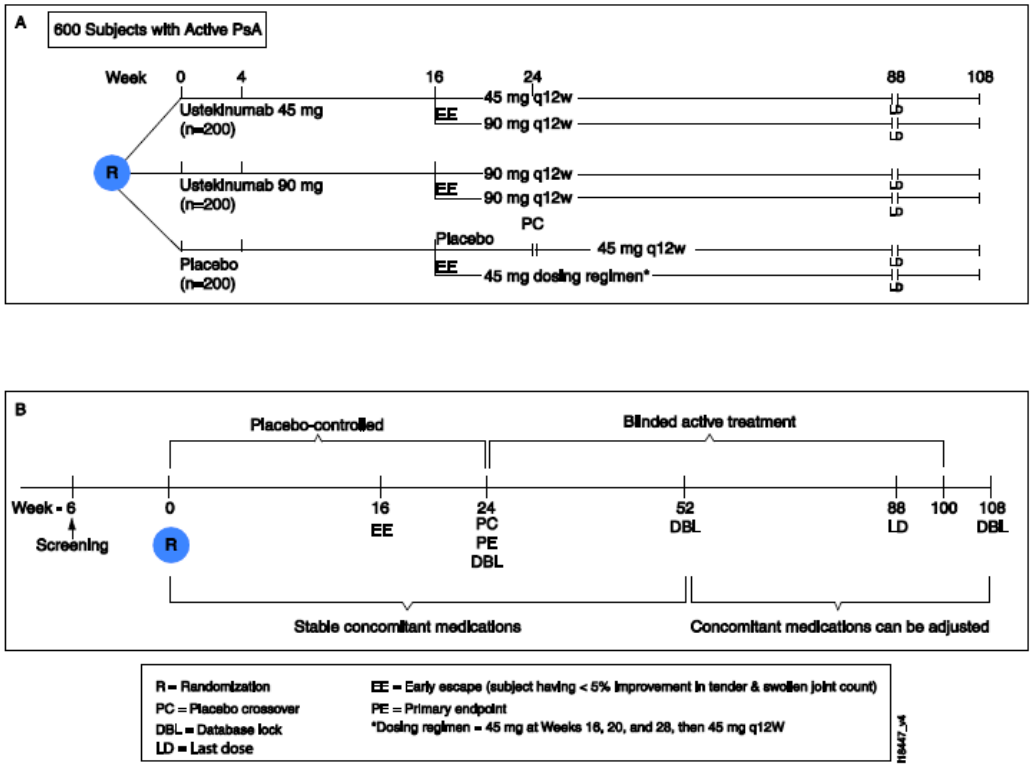
The primary efficacy objective of the PSUMMIT I Study was to demonstrate the efficacy of USK (given by SC injection at the dose of 45 mg q12w or 90 mg q12w after loading doses at Weeks 0 and 4) on the signs and symptoms of active PsA at 24 weeks. The secondary efficacy objectives of the study included the assessment of the effects of USK upon functional indices, structural damage, health related QOL and psoriatic skin disease (at 24 and 52 weeks).

The study was conducted at 104 sites in 14 countries in Europe, North America and Australia-New Zealand: USA (23 sites), Canada (19 sites), Russia (12 sites), Poland (8 sites), United Kingdom, Germany and Hungary (6 sites each), Australia (5 sites), New Zealand and Lithuania (4 sites each) Spain, Austria and Finland (3 sites each) and Latvia (2 sites). In the PSUMMIT I Study, the first subject was enrolled on 30 November 2009, and the last subject procedure for this efficacy dataset occurred on 27 October 2011.

The PSUMMIT I Study had a screening phase of up to 6 weeks. At baseline, 600 subjects were planned to be randomly assigned 1:1:1 to receive treatment with USK 45 mg, USK 90 mg, or placebo injections at Weeks 0 and 4 followed by q12w (every 12 weeks) dosing thereafter. During the 24-week placebo-controlled period, assessments were scheduled to occur every 4 weeks. Patients randomised to placebo therapy initially, were crossed-over to active treatment with USK 45 mg injections at Weeks 24 and 28, followed by q12w dosing thereafter. For USK treated subjects (45 and 90 mg groups) placebo injections were given at Weeks 20 and 24 to maintain blinding over the first 24 weeks of study follow-up. The last dose of study medication was to be administered at Week 88, and subjects were to be followed for efficacy up to week 100 and for safety up to week 108. Database locks were scheduled to occur at Weeks 24, 52 and 108. This submission includes the study report up to Week 52. The trial schema for the PSUMMIT I Study (up to week 108) is presented in Figure 1.

The study design also allowed for early escape in patients failing to sufficiently improve. This is appropriate for ethical reasons. 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 without re-randomisation. All of the placebo escape patients received USK 45 mg at Weeks 16, 20 and 28 followed by 45 mg q12w thereafter, with the last dose to be given at Week 88. For those subjects in the USK 45 mg cohort who qualified for early escape therapy, USK 90 mg was commenced at Week 16, followed by 90 mg q12w thereafter (last dose at Week 88). Subjects in the USK 90 mg treatment group who qualified for escape treatment at Week 16, continued with USK 90 mg injections for the duration of their participation in the study.

Figure 1: Study Schema for PSUMMIT I



There were 4 amendments to the original protocol. The first amendment was instituted before the commencement of patient enrolment, and all of the other amendments occurred after. The amendments contained clarifications about baseline assessments, efficacy measures and minor safety related issues. Two of the changes with amendment 3 (27 October 2010) are noteworthy. The screening CRP criterion of ≥ 0.6 mg/dL was decreased to ≥ 0.3 mg/dL. The sponsor states the lower qualifying CRP value is more reflective of the PsA population. Secondly, the inhibition of structural damage objective/endpoint was moved from a co-primary objective/endpoint to a major secondary objective/endpoint. The corresponding information about the power calculation and sample size determination for the structural change endpoint was removed from the protocol. These 2 amendments have the potential to have impacted on the integrity of the study's outcomes.

7.1.1.1.2. Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be between 18 and 99 years of age with a diagnosis of PsA at least 6 months prior to the first administration of study medication, and who have active disease despite current or previous DMARD and/or NSAID therapy. Subjects were required to have active arthritis at baseline and screening as defined by ≥ 5 tender and swollen joints, and a C-reactive protein [CRP] reading ≥ 0.3 mg/dL at screening (≥ 0.6 mg/dL prior to protocol amendment 3). No concomitant DMARD use with the exception of MTX (not exceeding 25 mg/week, either oral or parenteral, and at a stable dose for at least 4 weeks prior to the first administration of study medication) was permitted at entry and during the study; however, all NSAID use was allowed. Prior DMARD treatment was defined as taking such therapy for at least 3 months, or evidence of DMARD intolerance. NSAID therapy was defined as taking an NSAID for at least 4 weeks, or evidence of intolerance. Subjects were also required to have either active psoriatic skin lesions or a documented history of plaque psoriasis.

The exclusion criteria were extensive and involved 5 domains. If patients met any 1 of the criterion they were to be excluded from the study.

- Diagnosis – any other inflammatory arthritis or other autoimmune rheumatic disorder such as RA, Ankylosing Spondylitis and Lupus; and pregnancy/lactation
- Past history – substance abuse (drug or alcohol); history of chronic or recurrent infections (such as bronchiectasis, cystitis, or skin wounds), recent serious or life-threatening infection within 2 months of the baseline visit, Herpes Zoster infection within the last 2 months, or any current sign or symptom that may have indicated an infection; known TB disease, high risk of acquiring TB, or latent TB infection; high risk of infection in the investigator's opinion (such as subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections); history of an infected joint prosthesis at any time; concurrent infection with Hepatitis B or C virus or HIV; lymphoproliferative disorder; and malignancy within the last 5 years (except for excised basal or squamous cell skin cancers or cervical carcinoma in situ successfully treated by surgery)
- Abnormal baseline laboratory results – liver function tests > 1.5 x Upper Limit Normal (ULN), serum creatinine > 1.5 mg/dL, total white blood cell count < 3.5 x 10^9/L, neutrophil count < 1.5 x 10^9/L, platelet count < 100 x 10^9/L, or haemoglobin < 8.5 g/dL
- Recent or concurrent treatments - use of conventional DMARD therapy within 4 weeks prior to baseline (12 weeks for LEF), oral prednisone > 10 mg/day (as well as, intra-articular or parenteral CS within 4 weeks), phototherapy for skin psoriasis within 4 weeks prior to baseline, topical therapy for skin psoriasis within 2 weeks of baseline, any live virus or bacterial vaccination within 3 months of baseline, or lithium within 4 weeks of baseline; and
- Prior treatment – any exposure to anti-TNF treatment or abatacept; as well as natalizumab, efalizumab or any drugs that deplete B or T-cells within the last 12 months (for example, rituximab and alemtuzumab).

7.1.1.1.3. Study treatments

Subjects were randomised in a 1:1:1 ratio to receive USK 45 mg, USK 90 mg, or placebo injections. USK was supplied in single use, pre-filled syringes with a 27-gauge, 1/2-inch fixed needle. There were 2 dose strengths (that is, 90 mg in 1 mL nominal volume or 45 mg in 0.5 mL nominal volume).

Placebo injections were supplied in an identical presentation. At the study site, the pre-filled syringes of USK solution were stored in a secured refrigerator at 2°C to 8°C and were protected from light. There is no comment in the study report about how differences in viscosity between USK and placebo injections may have affected blinding. All injections were given by SC injection into the lateral abdominal wall or upper outer thigh. During each dosing visit where 2 injections were administered, 2 different anatomical sites were injected. During the double-blind phase of the trial, study treatments (including placebo injections) were administered by trained study centre personnel and patients did not self-administer therapy.

Concurrent treatment with MTX (≤ 25 mg weekly) was permissible during the PSUMMIT I Study. The dose of MTX had to be stable for at least 4 weeks prior to baseline, and throughout the study period. The use of DMARD combination therapy was forbidden. Patients were also able to continue with low dose CS (maximum oral dose of 10 mg/day of prednisone or equivalent) if they had been receiving a stable dose for at least 2 weeks prior to baseline. Similarly, NSAID (including COX-2 inhibitors) could be continued if these treatments were stable for at least 2 weeks prior to baseline. Analgesic medications (including paracetamol) were permitted except for ad hoc use within 24 hours prior to any scheduled study assessments. Phototherapy and/or topical agents for psoriasis (including low potency topical CS [2.5% concentration or less of hydrocortisone cream or equivalent]) were also allowed. However, CS injections for active PsA were not permitted.

7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- American College of Rheumatology (ACR) response criteria
- Disability Index of the HAQ (Health Assessment Questionnaire)
- Psoriasis Area and Severity Index (PASI), and
- Radiographic Response – assessed by the change from baseline over time in the modified van der Heijde-Sharp (vdH-S) score.

The primary efficacy outcome in the PSUMMIT I Study was the proportion of subjects achieving an ACR20 response at Week 24. This endpoint is appropriate for evaluating the effect of treatment on the signs and symptoms of PsA. The ACR response criterion is a composite endpoint, which quantifies the clinical response to therapy in patients with RA and PsA. A patient with an ACR20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen (maximum of 66) and tender (maximum of 68) joint counts, as well as a 20% improvement in any 3 of the 5 core-set measures which include Patient's Global Assessment, Physician's Global Assessment of disease activity, Patient's Assessment of Pain score (on 10 cm VAS), Patient's assessment of physical function as measured by the HAQ-DI, and acute phase reactants (ESR or CRP; in this study CRP was used). The analyses of ACR50 and ACR70 included the same criteria as ACR20, but with the use of a higher percentage improvement (50% or 70%) instead of 20%.

Major secondary endpoints (all assessed at Week 24) in the order of statistical testing were:

- Change from baseline in the HAQ-DI score
- Proportion of subjects (with baseline ≥ 3% body surface area [BSA] psoriatic involvement) who achieve a PASI 75 response
- Proportion of subjects with ACR50 response
- Proportion of subjects with ACR70 response, and
- Mean change from baseline in the total vdH-S score. The radiographic data collected in the PSUMMIT I and II studies were pooled for analysis, and will be presented in section 7.1.3 of this report (Weeks 24 and 52 results).

The HAQ-DI is a validated method for measuring disability in inflammatory arthritis (range: 0-3 with higher score indicating more functional impairment). It assesses physical function by measuring the patient's ability to perform the following 8 activities (using 20 questions): - dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity. The measure uses a scale ranging from zero (best) to three (worst). A change in the HAQ-DI of - 0.30 units is considered to be the minimal clinically important difference (MCID) in treatment studies of patients with PsA (Mease et al, 2004).

The Psoriasis Area and Severity Index (PASI) is an assessment of 4 anatomic sites (head, upper extremities, trunk, and lower extremities) for erythema, induration, and desquamation using a scale of zero (the best evaluation, no symptoms) to four (the worst evaluation, very marked). The extent of lesions in a given area is assigned a numerical value from one (< 10%) to six (90 - 100%). The PASI score is then calculated from a weighted average based on the % of body surface area (BSA) of the anatomic site (head, 10%; upper extremities, 20%; trunk, 30%; and lower extremities, 40%). The PASI score has a range from 0 (no disease) to 72 (maximal disease), and responses can be based on at least 50%, 75%, 90% and 100% improvement in scores from baseline.

There were a very large number of other non-key secondary efficacy outcomes (grouped below by disease manifestation/category) all assessed at Weeks 24 and 52, which included:

- Proportion of patients achieving ACR20/50/70 response over time
- Physical Function - Proportion of subjects with HAQ-DI response
- Other clinical features of PsA – Percentage change from baseline in enthesitis and dactylitis scores, proportion of patients achieving Psoriatic Arthritis Response Criteria (PsARC)
- DAS28 remission (using CRP), and various levels of BASDAI response (20, 50, and 70)
- Skin Effects – proportion of subjects with PASI90 and PASI100 responses, and
- Heath-related outcomes - Change from baseline in SF-36 scores as well as DLQI, and health economics.

Enthesitis was assessed using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), modified for PsA, which assesses 15 core axial sites (for example, bilateral first and seventh costochondral joints, and proximal insertion of the Achilles tendon, but not the plantar fascia insertions into the calcaneus) in a dichotomous 0/1 score for tenderness. The index has a score range of 0 - 15. The presence and severity of dactylitis was assessed in both hands and feet (n = 20 digits) using a scoring system for each site ranging from 0 - 3 (with 0 = no, 1 = mild, 2 = moderate and severe dactylitis). The dactylitis score has a range from 0 - 60. Unlike the HAQ-DI score, there is no validated acceptance of what constitutes the MCID in enthesitis and dactylitis score.

The Psoriatic Arthritic Response Criteria (PsARC) contains a variation of 4 of the measures of the ACR 20 response (Swollen and Tender joint counts; as well as the Physician's and Patient's Global Assessment of Disease Activity) but does not include a measure of pain, function/disability, or an acute phase reactant (ESR or CRP). PsARC response is defined as no worsening in any of the criteria listed below, and an improvement from baseline in at least 2 of the following 4 criteria, one of which has to be either the tender or swollen joint count:

- Physician's Global Assessment of Disease Activity (PhGADA; decrease by 1 point in the 5-point Likert scale)
- Patient's Global Assessment of Disease Activity (PtGADA; decrease by 1 point in the 5-point Likert scale)
- Tender Joint Count (at least 30% improvement in the 68 joint count), and
- Swollen Joint Count (at least 30% improvement in the 66 joint count).

Worsening of criteria is defined as > 20% increase for global assessments, and > 30% increase for joint counts.

The BASDAI is a validated, self-reported instrument consisting of 6 questions (all rated on a 10 cm horizontal line) relating to fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration) over the last week. The BASDAI score correlates highly with the patient global assessment, but less so with the physician global assessment of disease activity. To give each symptom equal weighting, the mean of the 2 scores relating to morning stiffness (questions 5 and 6) is taken. The resulting 0 - 50 score is divided by 5 to give a final 0 - 10 BASDAI score. Higher scores indicate greater disease severity, and an overall score of 4 or more (out of 10) indicates active inflammatory spondylitis. A clinically meaningful response is defined as a 50% decrease (improvement) in the score over a time period of at least 12 weeks (that is, a BASDAI 50 response). The BASDAI score has only been validated in patients with AS, and not PsA.

The 28 joint Disease Activity Score (DAS28) is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA and PsA. It is a composite disease activity index of 4 clinical variables involving the tender joint count (up to 28 joints), swollen joint count (up to 28 joints), CRP, and the patient's assessment of general health

using a 10 cm visual analogue scale. The final score is derived by a complex mathematical calculation of the individual elements. DAS28 has a scale from 0 to 10, and most scores range from around 2 to a maximum of 10. According to EULAR guidelines, DAS28 > 5.1 indicates high disease activity, < 3.2 indicates low disease activity, and 'clinical remission' is indicated by a DAS28 score of < 2.6.

The SF-36 is a generic health assessment questionnaire intended to measure general health concepts not specific to any age, disease, or treatment group. This instrument has been validated in patients with PsA. It measures 8 health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. It also can be subdivided into two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores. An improvement of ≥ 5 points in the PCS or MCS is defined as a clinically meaningful improvement.

The DLQI is a 10-item questionnaire developed as a measure of disability for a wide range of dermatological conditions. It assesses the patient's perspective on the impact of skin disease on daily living. The DLQI has 4 item response options (0 - 3) with the total score ranging from 0 - 30 (higher score indicates greater impact of skin disease upon daily living). An overall score of 0 - 1 indicates no effect on the patient's life, 2-5 equals small effect, 6 - 10 indicates moderate impact, 11 - 20 is consistent with large effect and 21 - 30 represents an extremely large impact. The DLQI has been validated in the assessment of psoriasis, and shows discrimination and responsiveness in PsA trials as well.

7.1.1.1.5. Randomisation and blinding methods

Subject randomisation at Week 0 was conducted using a centralised IVRS (Interactive Voice Response System), and stratified by 3 factors: investigational site, baseline weight (≤ 100 kg or > 100 kg) and baseline MTX use (yes/no). The randomisation method was minimisation with a biased-coin assignment in a 1:1:1 ratio (USK 45 mg, USK 90 mg, or placebo). This approach aimed to minimise the imbalance in the distribution of the number of subjects across treatment groups within the levels of each stratification factor. Subjects initially treated with USK 45 mg that qualified for escape treatment at Week 16 were switched to USK 90 mg injections, while those in the placebo group were switched to USK 45 mg injections. Those in the USK 90 mg group who reached the early escape threshold maintained their original treatment. For all early escape patients, treatment after Week 16 remained double-blinded.

To maintain the blind between Weeks 0 and 28, all subjects received 2 SC injections at 2 different anatomical locations at Weeks 0, 4, 16, 20, 24 and 28 as follows:

- USK 45 mg: 0.5 mL USK 90 mg/mL and 1.0 mL placebo injection
- USK 90 mg: 1.0 mL USK 90 mg/mL and 0.5 mL placebo injection
- Placebo group: 0.5 mL placebo injection and 1.0 mL placebo injection.

USK and placebo injections were presented in a similar manner of sterile, single use, prefilled syringes. However, as with all biological DMARDs there may have been differences in the viscosity of the USK and placebo injections, for which the study report does not make any particular statement about what special precautions may have been undertaken to ensure blinding. During the trial, study treatments (including placebo injections) were administered by pre-specified, trained study centre personnel with investigators and patients blinded to study treatment assignment.

7.1.1.1.6. Analysis populations

The primary analysis of all efficacy variables was performed using the randomised set of patients, which consisted of all subjects randomised into the trial, analysed by imputation of missing values if required.

7.1.1.1.7. Sample size

The PSUMMIT I Study was powered to detect significant treatment differences in reducing the signs and symptoms of PsA. With a total of 600 enrolled subjects (that is, 200 subjects in each treatment group), and assuming 50% MTX usage at baseline, a simulation of 5000 repetitions was used to calculate the power to detect a significant difference in the proportion of subjects achieving an ACR20 response using a CMH test with stratification by baseline MTX usage (yes/no). The study had over 99% power to detect a treatment difference ($\alpha = 0.05$) in the ACR20 response for at least one USK group compared with the placebo arm assuming a treatment effect size of 20 - 25% for subjects not receiving MTX, and 25 - 30% for subjects receiving MTX in achieving ACR20 response at Week 24. These assumptions were based on the data obtained in the Phase II PsA study, C0743T10.

7.1.1.1.8. Statistical methods

All statistical tests were 2-sided and performed at $\alpha = 0.05$. A sequential approach was undertaken to control for multiplicity for the primary and major secondary efficacy variables. The primary analysis compared the proportion of ACR20 responders in the combined USK group with the control arm. To maintain a Type error rate of 0.05, the pair-wise comparisons between each USK dose group and the placebo arm were performed after the combined USK group analysis showed a significant treatment effect in favour of USK versus placebo.

After the primary efficacy endpoint was achieved, a hierarchical test procedure was applied to the major secondary endpoints to protect the overall significance level for multiplicity. For each secondary endpoint, the test for the combined USK group was done first before each USK dose could then be compared to placebo. The pre-defined order of hypothesis testing, each at a 2-sided 5% alpha level for USK dose regimen versus placebo, was:

1. Change from baseline in HAQ-DI at Week 24
2. Proportion of patients achieving PASI 75 (with baseline ≥ 3% BSA psoriasis) at Week 24
3. Proportion of subjects with ACR50 response at Week 24
4. Proportion of patients with ACR70 response at Week 24, and
5. Mean change from baseline to Week 24 in the total vdH-S score of the hands and feet. The radiographic data was also analysed at 52 weeks, and X-ray data collected in the PSUMMIT I and II studies was pooled for analysis (see section 7.1.3 of this report).

Analyses suitable for categorical data such as the proportion of subjects achieving composite clinical endpoints (for example, proportion of subjects with an ACR20 response) were compared using the chi-square or Cochran-Mantel-Haenszel (CMH) test, adjusted for baseline MTX usage (yes/no). Continuous data such as HAQ-DI score and individual ACR components were compared using an analysis of covariance (ANCOVA) on the van der Waerden normal scores, adjusted for baseline MTX usage (yes/no).

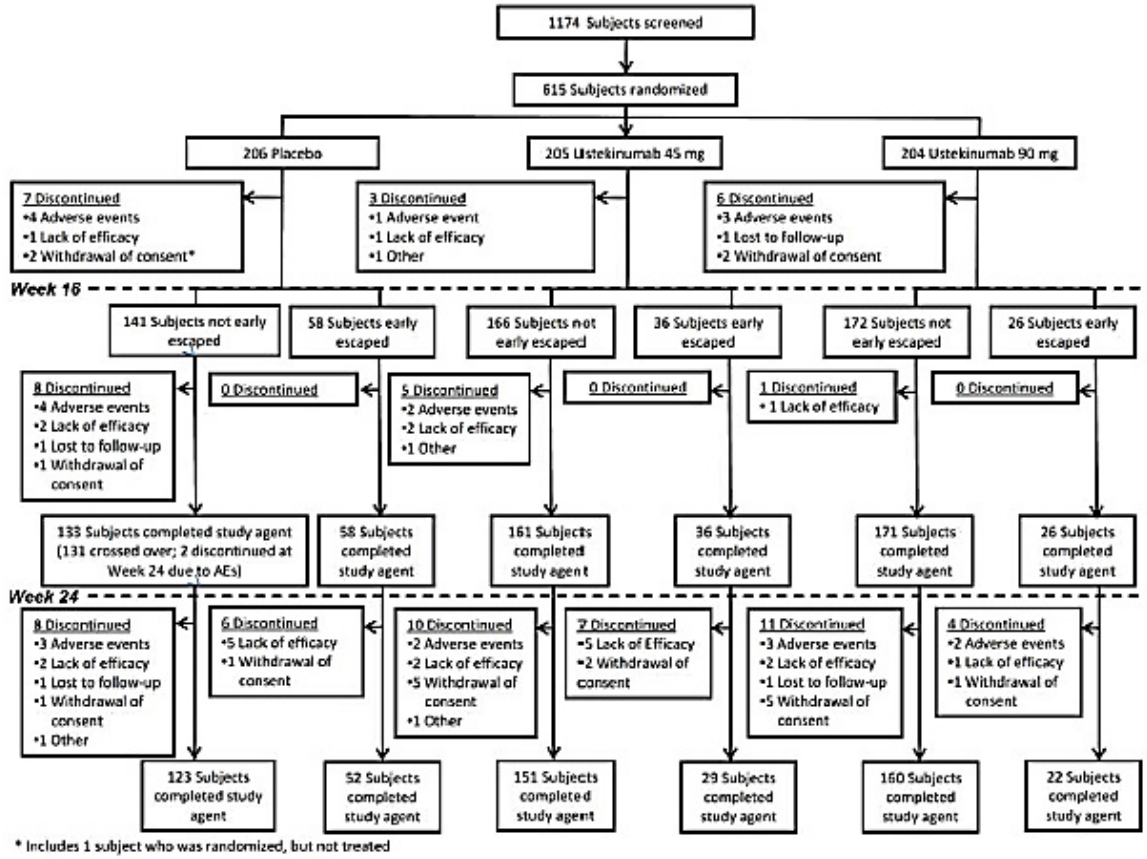
For the primary efficacy analysis, subjects who withdrew for any reason before Week 24 were considered non-responders. For the ACR response criteria, imputation of the last non-missing observation (including baseline values) was used for the handling of missing data. To test the robustness of the results from the main analysis of the primary clinical endpoint (ACR20 response at Week 24), sensitivity analyses were performed with the exclusion of subjects with incomplete ACR component data, and also with determining such patients as non-responders.

7.1.1.1.9. Participant flow

A total of 1174 patients were screened for enrolment in the PSUMMIT I Study, and 615 of these subjects were randomised to treatment at Week 0 (205 to the USK 45 mg group, 204 to the USK 90 mg arm, and 206 to placebo). All randomised subjects received their assigned treatment at Week 0 with the exception of 1 subject in the placebo group who withdrew consent and was

never treated. At Week 16, 58 of 205 (28.3%) subjects in the placebo group met the early escape criteria, and were switched to USK 45 mg injections; and 36 of 205 (17.6%) subjects randomised to USK 45 mg met the early escape criteria and began receiving USK 90 mg injections. Twenty-six of 204 (12.7%) subjects randomised to USK 90 mg qualified for escape, but as per the study protocol all continued to receive treatment with USK 90 mg injections until Week 24 – refer to Figure 2.

Figure 2: Subject Disposition in PSUMMIT I Study through to Week 52



At Week 24, a total of 30 subjects in the study had discontinued with a higher rate of withdrawal in the placebo group (7.3%; 15/206) than the USK 45 mg (3.9%; 8/205) and USK 90 mg (3.4%; 7/204) arms. The most common reason for discontinuation of study medication across all 3 treatment groups by Week 24 was adverse events (AE). A total of 6 subjects withdrew due to lack of efficacy (3 in the placebo arm, 2 in the USK 45 mg group and 1 in the USK 90 mg arm).

A total of 560 subjects (91.1% of 615) completed 52 weeks of treatment follow-up in the PSUMMIT I Study. Of the 55 patients who discontinued study medication before 52 weeks, a higher proportion of those in the placebo group (11.2%; 23/206) did so, compared to the USK treatment arms (7.8% [16/205] in the 45 mg group and 7.8% [16/204] in the 90 mg arm). Withdrawal of consent was the most common reason for discontinuation in all of the treatment groups (7.6%; 47/615).

7.1.1.1.10. Major protocol violations/deviations

Of the 615 patients who were randomised into the PSUMMIT I Study, 42 (6.8%) were recorded as having potentially significant protocol deviations by Week 24: 7.3% (15/205) in the USK 45 mg group, 6.4% (13/204) in the USK 90 mg arm and 6.8% (14/206) in the placebo group. The most common types of protocol deviations were similar in type and incidence for each of the treatment groups and related to selection criteria not being met (3.4%; 21/615), receiving

incorrect study medication or dose (2.0%; 12/615) and missed study drug administration (1.8%; 11/615).

7.1.1.1.11. Baseline data

The treatment groups were well balanced with respect to demographic characteristics. Overall, subjects had a mean and median age of 47 - 48 years (range: 18 - 81 years), just over half (53.7%; 330/615) were male, and the majority (96.6%; 593/615) were of Caucasian ethnicity. The overall mean BMI was 30.5 kg/m^2, and the majority of subjects (75.0%; 461/615) had a baseline weight of ≤ 100 kg (median weight 86 kg). Published data shows that patients with PsA have an increased incidence of being overweight or obese compared to age and gender matched population controls. Less than half of all subjects (41.3%; 254/615) reported current alcohol consumption (median weekly consumption of 2 standard drinks), and 19.8% (122/615) were current tobacco users (median daily cigarette use of 12). By geographic region, the largest percentage of patients came from Europe (64.6%; 397/615), followed by North America (28.5%; 175/615) and Australia-New Zealand (7.0%; 43/615).

The treatment groups were similar with respect to baseline PsA features. The mean duration of PsA for all subjects was 6.58 years (median 4.03 years, range: 0.4 - 47.3 years). A longer median duration of PsA was observed in the USK 90 mg group (4.92 years) compared to the placebo (3.64 years) and USK 45 mg arms (3.38 years). Expectedly, the median duration of psoriasis was substantially longer in all of the treatment groups (overall 13.2 years). In the PSUMMIT I Study, the subtype of PsA (as defined by the investigator) was recorded at baseline. The majority of patients had either polyarticular arthritis (37.9%; 233/615) or spondylitis with peripheral arthritis (30.1%; 185/615). Asymmetric peripheral arthritis affected 19.8% (122/615) of enrolled subjects, and was recorded in a higher proportion of USK treated patients (22.4% [46/205] for the 45 mg group and 23.5% [48/204] for the 90 mg arm) compared to the placebo group (13.6%; 28/206). Isolated DIP joint arthritis was uncommon (11.5%; 71/615) and arthritis mutilans was rare (0.7%; 4/615). Most patients had ≥ 3% BSA skin psoriasis at baseline (71.7%; 440/615) and this was recorded at a similar frequency between the 3 treatment arms. In addition, 71.7% (441/615) of all subjects had evidence of enthesitis at baseline, and 48.1% (296/615) had current dactylitis. The incidence of patients suffering enthesitis and dactylitis at baseline in the PSUMMIT I Study is considerably higher than that recorded in the anti-TNF drug trials in subjects with active PsA. All of these disease manifestations occurred at a similar incidence across the treatment groups.

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were similar for the USK 45 mg (22.19 and 12.49, respectively) and USK 90 mg (23.20 and 12.91, respectively) groups, but slightly higher in the placebo arm (25.09 and 15.02, respectively) – refer to Table 3. The mean HAQ-DI scores were similar between the 3 treatment groups at 1.22-1.24, and consistent with moderate disease activity. The mean CRP for all subjects was elevated at 16.93 mg/L.

Regarding concurrent skin psoriasis at baseline, the majority of subjects in each of the 3 treatment groups had ≥ 3% BSA psoriasis skin involvement: 70.9% (146/206) in the placebo group, 70.7% (145/205) in the USK 45 mg arm and 73.0% (149/204) in the USK 90 mg group. At baseline, the mean PASI score (with range) was slightly lower in the USK 45 mg group (7.1 [3.3 - 15.3]) compared to the placebo (8.8 [4.4 - 14.3]) and the USK 90 mg groups (8.4 [4.8 - 14.7]). The mean baseline DLQI scores were similar between the treatment groups: 11.0 (5.0 - 18.0) in the placebo group, 10.0 (5.0 - 16.0) in the USK 45 mg arm and 9.0 (5.0 - 16.0) in the USK 90 mg group.

The incidence of relevant co-morbid conditions was similar in the treatment groups. Published data shows that patients with PsA have an increased rate of cardiovascular disease and risk factors. Regarding risk factors for cardiovascular disease a past history of hypertension was recorded in 36.1% of all subjects, 14.0% reported hyperlipidaemia and 11.1% recorded

diabetes mellitus. Past history of depression was recorded in 11.2% of patients. Hospitalisation in the last 12 months was reported in 14.6% of subjects, including 3.1% of patients having a prior hospitalisation for infection.

Table 3: Baseline Activity of Psoriatic Arthritis in PSUMMIT I Study (Randomised Subjects)

		Ustekinumab			
	Placebo	45 mg	90 mg	Combined	Total
Subjects randomized	206	205	204	409	615
Number of swollen joints (0-66)					
N	206	205	204	409	615
Mean (SD)	15.02 (10.213)	12.49 (7.773)	12.91 (8.308)	12.70 (8.037)	13.48 (8.886)
Median	12.00	10.00	10.00	10.00	10.00
IQ range	(8.00; 19.00)	(7.00; 15.00)	(7.00; 16.00)	(7.00; 15.00)	(7.00; 17.00)
Range	(4.0; 56.0)	(5.0; 54.0)	(4.0; 54.0)	(4.0; 54.0)	(4.0; 56.0)
Number of tender joints (0-68)					
N	206	205	204	409	615
Mean (SD)	25.09 (15.049)	22.19 (13.914)	23.20 (13.677)	22.69 (13.789)	23.49 (14.256)
Median	22.00	18.00	20.00	19.00	20.00
IQ range	(13.00; 33.00)	(12.00; 28.00)	(12.00; 32.00)	(12.00; 29.00)	(12.00; 30.00)
Range	(5.0; 68.0)	(5.0; 68.0)	(5.0; 67.0)	(5.0; 68.0)	(5.0; 68.0)
Patient's assessment of pain (VAS; 0-10 cm)					
N	206	205	204	409	615
Mean (SD)	6.10 (2.013)	6.30 (1.911)	6.40 (1.935)	6.35 (1.921)	6.26 (1.954)
Median	6.40	6.50	6.70	6.60	6.60
IQ range	(4.80; 7.60)	(5.10; 7.60)	(5.05; 7.80)	(5.10; 7.70)	(5.00; 7.70)
Range	(0.2; 10.0)	(0.7; 9.9)	(1.5; 9.9)	(0.7; 9.9)	(0.2; 10.0)
Patient's global assessment of disease activity (VAS; 0-10 cm)					
N	206	205	204	409	615
Mean (SD)	5.82 (1.803)	5.71 (1.777)	6.07 (1.743)	5.89 (1.768)	5.86 (1.778)
Median	5.85	5.70	6.30	6.00	6.00
IQ range	(4.60; 7.30)	(4.40; 7.00)	(4.85; 7.35)	(4.60; 7.10)	(4.60; 7.20)
Range	(1.3; 9.9)	(1.2; 9.9)	(0.6; 9.7)	(0.6; 9.9)	(0.6; 9.9)
Physician's global assessment of disease activity (VAS 0-10 cm)					
N	206	205	204	409	615
Mean (SD)	6.05 (1.974)	6.24 (1.914)	6.55 (1.840)	6.39 (1.881)	6.28 (1.918)
Median	6.40	6.50	6.80	6.60	6.50
IQ range	(4.90; 7.50)	(5.00; 7.60)	(5.30; 7.90)	(5.10; 7.80)	(5.00; 7.70)
Range	(0.2; 10.0)	(1.1; 9.9)	(0.8; 9.9)	(0.8; 9.9)	(0.2; 10.0)
HAQ-DI score (0-3)					
N	204	205	204	409	613
Mean (SD)	1.24 (0.647)	1.22 (0.610)	1.22 (0.634)	1.22 (0.622)	1.23 (0.630)
Median	1.25	1.25	1.25	1.25	1.25
IQ range	(0.75; 1.75)	(0.75; 1.75)	(0.75; 1.63)	(0.75; 1.75)	(0.75; 1.75)
Range	(0.0; 2.8)	(0.0; 2.8)	(0.0; 2.8)	(0.0; 2.8)	(0.0; 2.8)
CRP (mg/L)					
N	206	205	204	409	615
Mean (SD)	15.93 (19.051)	16.88 (17.831)	17.99 (18.038)	17.43 (17.921)	16.93 (18.306)
Median	9.63	9.95	12.30	11.20	10.30
IQ range	(5.98; 18.60)	(5.87; 21.10)	(6.48; 21.65)	(6.05; 21.20)	(5.98; 20.70)
Range	(0.2; 177.0)	(0.3; 120.0)	(0.4; 130.0)	(0.3; 130.0)	(0.2; 177.0)

Overall, the majority of subjects (79.5%; 489/615) had received previous DMARD treatment, and the pattern of prior DMARD use was similar in each of the treatment groups. Most subjects (72.0%; 443/615) had prior use of only 1 - 2 DMARDs, but 7.5% (46/615) had experienced > 2 previous DMARDs, reflecting a treatment refractory PsA population. The 2 most commonly used prior DMARDs were MTX (74.8%; 460/615) and SSZ (22.1%; 136/615). Among subjects with prior exposure to MTX, one quarter (24.4%; 150/615) had taken MTX for at least 3 years. The majority of patients (89.2%; 547/615) in all treatment groups had a past history of taking NSAIDs, and one third (33.3%; 204/615) of subjects had previously taken low dose oral CS. No patient had a prior history of receiving anti-TNF drugs or anakinra. Only 2 subjects had prior exposure to biologic DMARDs – 1 case each of prior use of alefacept and efalizumab.

During the PSUMMIT I Study, 48.1% (296/615) of all patients continued MTX therapy. Use of concomitant MTX was slightly higher in the USK treated patients (48.3% [99/205] in the 45 mg group and 49.5% [101/204] in the 90 mg arm) compared to the placebo group (46.6%; 96/206). The median weekly dose of concurrent MTX used in all 3 groups was 15.0 mg (mean 15.7 - 16.5 mg; range: 7.5 - 25mg). In addition, the majority of patients (74.5%; 458/615) in all treatment groups took concomitant NSAID during the trial, and approximately one sixth (15.6%; 96/615) of subjects took low dose oral CS (median daily dose of 5 mg in the USK 90 mg and placebo groups, but 7.5 mg in the USK 45 mg arm).

7.1.1.1.12. Results for the primary efficacy outcome

At Week 24, a significantly greater proportion of subjects in the combined USK, USK 45 mg, and USK 90 mg groups (46.0% [188/409], 42.4% [87/205], and 49.5% [101/204], respectively) achieved an ACR20 response compared with subjects in the placebo group (22.8%; 47/206). Both p-values by either the re-randomisation test (primary analysis) or the CMH test (sensitivity analysis) were significant ($p < 0.001$) – refer to Table 4. A numerically higher ACR20 response rate at Week 24 was observed in the USK 90 mg group (49.5%) compared with the USK 45 mg arm (42.4%) but this was not statistically compared.

Table 4: Number and Proportion of Subjects achieving ACR20 Response at 24 Weeks in PSUMMIT I Study (Randomized Subjects)

		Ustekinumab		
	Placebo	45 mg	90 mg	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.

Sensitivity analyses were also conducted to test the robustness of the primary endpoint analysis, and to assess the impact of missing data. All of the sensitivity analyses showed results consistent with the main analysis outcome, thereby supporting the claim that the main analysis results were robust and not impacted by the data handling rules for missing data. One additional analysis was also conducted to assess the impact of early escape when the early escape rules were not implemented. As expected, the ACR20 response rate increased across all 3 treatment groups as compared with the main analysis, particularly in the placebo group, which reflects the early escape of placebo subjects to USK treatment. However, the ACR20 response rate was still statistically significant for subjects in the USK 45 mg and USK 90 mg groups compared with the placebo arm in this sensitivity analysis.

Study site did not affect the number of subjects who achieved an ACR20 response at Week 24. The number of subjects who achieved an ACR20 response by screening date (cut-off of 31 December 2010) was also considered. This cut-off date was chosen to approximate when protocol amendment 3 was implemented (that is, when the screening CRP was lowered from ≥ 0.6 mg/dL to ≥ 0.3 mg/dL). The majority of the subjects (approximately 75%) were enrolled prior to 31 December 2010. Regardless of enrolment before or after the 31 December 2010, consistently greater proportions of subjects in the USK 45 mg and 90 mg groups achieved ACR20 response at Week 24; however, the ACR20 response rates at Week 24 were higher across all 3 treatment groups among subjects enrolled after 31 December 2010, especially in the placebo group.

In addition, the 24-week ACR20 response rates observed in subjects receiving MTX at baseline (26.0%, 43.4%, and 45.5% in the placebo, USK 45 mg, and USK 90 mg groups, respectively), and those recorded in those not receiving MTX at baseline (20.0%, 41.5%, and 53.4% in the placebo, USK 45 mg and USK 90 mg groups, respectively) were similar.

7.1.1.1.13. Results for other efficacy outcomes

7.1.1.1.13.1. Change from Baseline to Week 24 in HAQ-DI score

Significantly greater improvements from baseline to Week 24 in HAQ-DI scores were observed in subjects in the combined USK, as well as the individual USK 45 mg and 90 mg groups (all showed a median change from baseline of - 0.25) compared with subjects in the placebo group (median change of 0). All of the pair-wise comparisons of active treatment versus placebo, by either the re-randomisation test or the test of analysis on the van der Waerden normal scores

(sensitivity analysis) were statistically significant (p < 0.001) – refer to Table 5. The mean improvement in HAQ-DI score at Week 24 was numerically higher in the USK 90 mg group (- 0.40) compared with the USK 45 mg group (- 0.31) but no formal statistical comparison was provided.

Table 5: Summary of Change from Baseline in HAQ-DI Score at Week 24 in PSUMMIT I Study.

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	206	205	204	409
Change from baseline				
N	206	205	204	409
Mean (SD)	-0.10 (0.390)	-0.31 (0.521)	-0.40 (0.514)	-0.36 (0.518)
Median	0.00	-0.25	-0.25	-0.25
IQ range	(-0.38; 0.13)	(-0.63; 0.00)	(-0.75; 0.00)	(-0.63; 0.00)
Range	(-1.4; 1.0)	(-1.9; 1.1)	(-2.4; 1.0)	(-2.4; 1.1)
p-value[a]		< 0.001	< 0.001	< 0.001
p-value[b]		< 0.001	< 0.001	< 0.001

[a] Based on the test of analysis of covariance on the van der Waerden normal scores.
[b] Based on re-randomization test.

At Week 24, USK treatment (combined 45 mg and 90 mg dose groups) resulted in greater improvement in HAQ-DI score than placebo treatment, regardless of MTX use at baseline. All comparisons for the improvement in HAQ-DI between the individual USK groups and the control arm were statistically significant in favour of USK, with the exception of the comparison between the USK 45 mg group and the placebo arm for subjects receiving MTX at baseline.

7.1.1.1.13.2. PASI 75 Response at Week 24

At 24 weeks, a significantly greater proportion of subjects with ≥ 3% BSA psoriasis skin involvement at baseline in the combined, 45 mg and 90 mg USK groups (59.9% [176/294], 57.2% [83/145] and 62.4% [93/149], respectively) achieved a PASI 75 response compared with subjects in the placebo group (11.0%; 16/146). All p-values for the pair-wise comparison of USK versus placebo were statistically significant (p < 0.001) – refer to Table 6. A numerically higher rate of PASI 75 response at Week 24 was observed in the USK 90 mg group (62.4%) compared with the USK 45 mg arm (57.2%).

Table 6: Number of Subjects achieving PASI 75 Response at 24 Weeks in PSUMMIT I Study (Randomized Subjects with ≥ 3% BSA skin psoriasis involvement at baseline).

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Randomized subjects with ≥ 3% BSA psoriasis skin involvement at baseline	146	145	149	294
PASI 75				
N	146	145	149	294
Subjects in response	16 (11.0%)	83 (57.2%)	93 (62.4%)	176 (59.9%)
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.

7.1.1.1.13.3. ACR50 and ACR70 Response Rates at Week 24

At Week 24, a significantly greater proportion of subjects in the combined USK group and in each of the individual USK groups achieved either an ACR50 or ACR70 response compared with the placebo group – refer to Table 7. P-values by either the re-randomisation test or the CMH chi-square test (sensitivity analysis) were statistically significant in favour of USK versus placebo. The ACR50 and ACR70 responses at 24 weeks were numerically higher in the USK 90 mg group compared with the USK 45 mg treated arm.

Table 7: Number of Subjects achieving ACR50 and ACR70 Response at 24 Weeks in PSUMMIT I Study (Randomized Subjects).

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Combined
Subjects randomized	206	205	204	409
ACR 50				
N	206	205	204	409
Subjects in response	18 (8.7%)	51 (24.9%)	57 (27.9%)	108 (26.4%)
p-value[a]		< 0.001	< 0.001	< 0.001
p-value[b]		< 0.001	< 0.001	< 0.001
ACR 70				
N	206	205	204	409
Subjects in response	5 (2.4%)	25 (12.2%)	29 (14.2%)	54 (13.2%)
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.

7.1.1.1.14. Other efficacy outcomes

7.1.1.1.14.1. ACR20/50/70 response rates at week 52

At Week 52, the proportion of subjects treated with USK (either dose) achieving an ACR20/50/70 response was maintained to that observed at Week 24. For those receiving USK 45 mg, the rate of ACR20 response at 52 weeks was 55.7% (108/194), ACR50 response was 31.4% (61/194) and the ACR70 response rate was 18.0% (35/194). For those subjects assigned to the USK 90 mg group, the rate of ACR20 response at 52 weeks was 60.3% (114/189), ACR50 response was 37.0% (70/189) and the ACR70 response rate was 21.2% (40/189).

For patients treated with USK at entry, ACR responses at Week 52 were also analysed by subject weight at baseline (> 100 kg versus ≤ 100 kg). For subjects weighing ≤ 100 kg (n = 307), ACR response rates are similar regardless of whether USK 45 mg or 90 mg injections are used – refer to Table 8. However, for subjects weighing > 100 kg (n = 102), the USK 90 mg dose shows a significant numerical advantage over the USK 45 mg dose in the various levels of ACR response at 52 weeks. Concomitant MTX use did not appear to affect the rates of ACR response in either of the USK treatment groups; however, these results should be cautiously interpreted, as the use of MTX was not randomly assigned.

Table 8: ACR Response Rates at 52 Weeks in PSUMMIT I Study (Randomized Subjects stratified according to subject weight at baseline).

	Randomized subjects with weight ≤100 kg at baseline		Randomized subjects with weight >100 kg at baseline	
	Ustekinumab			
	45 mg	90 mg	45 mg	90 mg
Number of subjects	153	154	52	50
Subjects in response				
N	146	144	48	45
ACR 20	90 (61.6%)	90 (62.5%)	18 (37.5%)	24 (53.3%)
ACR 50	53 (36.3%)	57 (39.6%)	8 (16.7%)	13 (28.9%)
ACR 70	31 (21.2%)	34 (23.6%)	4 (8.3%)	6 (13.3%)

At Week 24, patients in the placebo group were commenced on USK 45 mg injections, and their rate of ACR response at 52 weeks significantly increased compared to that observed at Week 24. For the subjects in the placebo to USK 45 mg cohort, the rate of ACR20 response at 52 weeks was 65.2% (120/184), ACR50 response was 38.0% (70/184) and the ACR70 response rate was 16.3% (30/184).

7.1.1.1.14.2. HAQ response over time

At Week 24, a higher proportion of subjects treated with USK achieved a clinically meaningful (≥ 0.3) improvement in their HAQ-DI score from baseline than those in the placebo group (47.8% [98/205] in the USK 45 mg group and 47.5% [97/204] in the USK 90 mg arm versus

28.8% [58/206] in the placebo arm; p-value < 0.001 for the pair-wise comparison of placebo to the combined USK cohort as well as each individual USK dose group). At Week 52, the proportion of HAQ responders was maintained in those treated with USK (47.4% in the 45 mg group and 51.3% in the 90 mg arm), and after initiation of USK 45 mg in the placebo group the proportion of HAQ responders was 52.8%.

At Week 52, the median change from baseline in the HAQ-DI score was - 0.25 in the USK 45 mg group and - 0.38 in the USK 90 mg arm. After initiation of USK 45 mg injections at Week 24, the median change from baseline in the HAQ-DI score for those in the original placebo group was - 0.38 at Week 52, which is similar to that observed in the group that received USK 45 mg injections from the beginning of the trial.

7.1.1.1.14.3. Enthesitis and dactylitis at weeks 24 and 52

At baseline, 71.7% (441/615) of all randomised subjects reported enthesitis. At 24 weeks, the proportion of subjects with documented ongoing enthesitis was statistically lower in the USK 45 mg group (68.6% [96/140]; p = 0.018) and the USK 90 mg arm (60.8% [90/148]; p < 0.001) compared with the placebo group (81.0%; 111/137). Furthermore, for subjects with enthesitis at baseline, significant median percentage improvements at Week 24 in the MASES score were observed for the USK 45 mg group (median improvement of 42.86% from a baseline score of 4.0; p = 0.002) and the USK 90 mg arm (median improvement of 50.0% from a baseline score of 5.0; p < 0.001) compared with the placebo group (zero median percentage improvement from a baseline score of 4.0). The median percentage improvement in the MASES score was slightly higher in numerical terms for the USK 90 mg group compared to the USK 45 mg arm, but a formal pair-wise statistical analysis of the 2 USK treatment regimens was not presented.

At Week 52, among the subjects with enthesitis at baseline, the percentage of USK treated patients with ongoing documented enthesitis was 55.6% in the 45 mg dose group and 54.2% in the 90 mg arm. In the placebo to USK 45 mg dose switch group, the proportion of subjects with enthesitis at Week 52 was 51.6%. At Week 52, the median percentage improvement in the modified MASES index was 83.3% in the USK 45 mg dose group and 74.2% in the USK 90 mg arm. For the placebo to USK 45 mg dose switch cohort, the median percentage improvement from baseline to Week 52 was 87.5%.

At baseline, just under half of all randomised subjects (48.1%; 296/615) recorded at least 1 digit with dactylitis. At Week 24, the proportion of subjects with ongoing dactylitis in 1 or more digits was significantly lower in the USK 45 mg group (56.6% [56/99]; p = 0.005) and USK 90 mg arms (55.8% [53/95]; p = 0.004) compared with the placebo group (76.1%; 70/92). In addition, for subjects with dactylitis at baseline, significant median percentage improvements at Week 24 in the dactylitis score were observed in the USK 45 mg (median improvement of 75.0% from a baseline score of 4.0) and USK 90 mg groups (median improvement of 70.83% from a baseline score of 4.0) compared with the placebo group (zero median percentage improvement from a baseline score of 4.5; p < 0.001 for both pair-wise comparisons of USK versus placebo). Comparable improvement in dactylitis (both in terms of proportion and extent) was observed in both the USK 45 mg and 90 mg dose groups.

At Week 52, among the subjects with dactylitis at baseline, the percentage of USK treated patients with ongoing documented dactylitis was 39.2% in the 45 mg dose group and 46.2% in the 90 mg arm. In the placebo to USK 45 mg dose switch group, the proportion of subjects with dactylitis at Week 52 was 40.7%. At Week 52, the median percentage improvement in the dactylitis score was 100% in all 3 treatment groups (USK 45 mg and 90 mg arms, as well as the placebo to USK 45 mg dose switch group).

7.1.1.1.14.4. PsARC response rates at weeks 24 and 52

Higher proportions of subjects in the USK treatment groups achieved PsARC response at Week 24 compared with the placebo group, and the response rate was maintained from Week 24 through to Week 52. The proportion of subjects achieving PsARC response at Week 24 was

56.1% (115/205) in the USK 45 mg group and 64.7% (132/204) in the USK 90 mg compared to 37.4% (77/206) in the placebo group ($p < 0.001$ for the comparison between each USK dose group and the combined USK cohort versus placebo). At Week 52, the rate of PsARC response was 73.2% in the USK 45 mg group and 74.6% in the USK 90 mg arm. For the placebo to USK 45 mg dose switch group (at Week 24), the rate of PsARC response at 52 weeks was 75.5%.

7.1.1.1.14.5. DAS28 remission rate at weeks 24 and 52

At 24 weeks, a greater proportion of subjects treated with USK (20.5% [42/205] in the 45 mg dose group and 19.6% [40/204] in the 90 mg arm) achieved DAS28 remission compared to those treated with placebo injections (8.3% [17/206]; $p < 0.01$ for both comparisons of USK versus placebo).

At Week 52, the proportions of patients in DAS28 remission in the USK 45 mg and 90 mg groups were 29.9% and 31.7%, respectively. After initiation of USK 45 mg at Week 24, the placebo arm showed a similar rate of DAS28 remission (29.3%; 54/184) at 52 weeks.

7.1.1.1.14.6. BASDAI response rates at week 24

At Week 24, a significantly higher proportion of subjects treated with USK achieved at least a 20% improvement from baseline in their BASDAI score compared with the placebo group. At Week 24, the BASDAI 20 response rate was 49.0% (25/51) in the USK 45 mg group ($p = 0.013$) and 58.3% (35/60) in the USK 90 mg arm ($p < 0.001$) compared with 26.2% (16/61) in the placebo group. The BASDAI 50 response rate was significantly higher in the USK 90 mg group (31.7% [19/60]; $p = 0.014$), but not in the USK 45 mg arm (23.5% [12/51]; $p = 0.122$) when compared with the control group (13.1%; 8/61). At Week 24, a significantly higher proportion of subjects treated with USK achieved a BASDAI 70 response: 13.7% (7/51) in the USK 45 mg group ($p = 0.003$) and 15.0% (9/60) in the USK 90 mg arm ($p = 0.002$) compared with no subjects in the placebo group achieving this level of response.

7.1.1.1.14.7. PASI response rates at weeks 24 and 52

As summarised in Table 9, the proportion of subjects with ≥ 3% BSA psoriasis skin involvement at baseline that achieved PASI 50/75/90 and PASI 100 responses through by Week 24 were significantly greater in subjects who received USK (either dose) as compared with the placebo group. In general, higher rates of PASI response were observed in USK treated subjects (either dose) who were not receiving concurrent MTX (versus taking MTX), and those weighing ≤ 100 kg at baseline (as opposed to patients weighing > 100 kg at baseline).

Table 9: Summary of PASI Responses at Week 24 in PSUMMIT I Study (Randomized Subjects with ≥ 3% psoriasis skin involvement at baseline).

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Combined
Randomized subjects with ≥ 3% BSA psoriasis skin involvement at baseline	146	145	149	294
PASI 50	35 (24.0%)	113 (77.9%)	115 (77.2%)	228 (77.6%)
p-value		< 0.001	< 0.001	< 0.001
PASI 75	16 (11.0%)	83 (57.2%)	93 (62.4%)	176 (59.9%)
p-value		< 0.001	< 0.001	< 0.001
PASI 90	4 (2.7%)	60 (41.4%)	65 (43.6%)	125 (42.5%)
p-value		< 0.001	< 0.001	< 0.001
PASI 100	2 (1.4%)	29 (20.0%)	41 (27.5%)	70 (23.8%)
p-value		< 0.001	< 0.001	< 0.001

PASI responses observed at Week 24 were maintained through to Week 52. For example, the proportion of subjects with PASI 75 response at 52 weeks was 70.1% (94/134) in the USK 45 mg group and 68.1% (96/141) in the USK 90 mg arm. For patients who switched from placebo to USK 45 mg injections at Week 24, the PASI 75 response rate at 52 weeks was 67.7%.

Another supporting efficacy endpoint was the proportion of subjects who achieved a combination of skin and joint responses (PASI 75 and ACR20 response) at Week 24. A significantly greater proportion of USK treated subjects achieved this dual response (27.6% [40/145] for USK 45 mg and 41.6% [62/149] for USK 90 mg) compared to those in the control arm (5.5% [8/146]; $p < 0.001$ for both comparisons).

7.1.1.1.14.8. Health related QOL outcomes at weeks 24 and 52

In the subset of patients with ≥ 3% BSA psoriasis skin involvement and reporting a DLQI score > 1 at baseline, significantly higher proportions of subjects in the USK treatment groups at Week 24 compared with the placebo arm recorded a DLQI score of 0 or 1 (that is, psoriasis considered to have no effect on the patient's life). At Week 24, the proportion of subjects with a DLQI score of 0 or 1 was 37.2% (54/145) in the USK 45 mg group and 53.0% (79/149) in the USK 90 mg arm compared with 8.3% (13/145) in the placebo group. At Week 52, the percentage of patients with a DLQI score of 0 or 1 was 47.2% in the USK 45 mg group and 55.8% in the USK 90 mg arm. For the placebo to USK 45 mg dose switch group (at Week 24), the proportion of patients with a DLQI score of 0 or 1 at 52 weeks was 45.5%.

At Week 24, the mean change from baseline in the SF-36 PCS scores was statistically greater in both USK treatment groups (4.89 point improvement for USK 45 mg from a baseline mean of 31.16 [n = 200], and 6.22 point improvement for USK 90 mg from a baseline mean of 31.45 [n = 197]) compared with the placebo group (1.15 point improvement from a baseline mean of 31.39 [n = 196]; $p < 0.001$ for both pair-wise comparisons). At Week 24, the proportion of subjects that achieved a clinically meaningful improvement (≥ 5 point improvement from baseline in the SF-36 PCS score) was significantly greater in the USK treatment groups compared with the control arm. At Week 24, the proportion of subjects with ≥ 5 point improvement from baseline in SF-36 PCS score was 46.5% (93/200) in the USK 45 mg group and 53.3% (105/197) in the USK 90 mg arm compared with 26.0% in the placebo group (51/196; $p < 0.001$ for both pair-wise comparisons). At 52 weeks, the mean improvement from baseline in the SF-36 PCS scores was 6.25 points for subjects treated with USK 45 mg and 6.46 points for those who received USK 90 mg injections.

At Week 24, the mean change from baseline in the SF-36 MCS scores was statistically greater in the USK 90 mg group (4.79 point improvement from a baseline mean of 43.48 [n = 197]) compared with the placebo group (1.53 point improvement from a baseline mean of 43.51 [n = 196]: $p < 0.001$). The change from baseline to Week 24 in the SF-36 MCS scores was numerically greater, but not statistically significant for the USK 45 mg dose group (3.35 point improvement from a baseline mean of 42.77 [n = 200]) compared with the control arm. At Week 24, the proportions of subjects that achieved a clinically meaningful cut-off (≥ 5 point improvement from baseline in SF-36 MCS score) were significantly greater in the USK 90 mg group compared with placebo ($p = 0.005$). The proportions of subjects that achieved a clinically meaningful cut-off in SF-36 MCS score were also numerically greater in the USK 45 mg dose group, but statistically non-significant ($p = 0.486$). At Week 24, the proportion of subjects with ≥ 5 point improvement from baseline in SF-36 MCS score was 37.0% (74/200) in the USK 45 mg group and 47.7% (94/197) of the subjects in the USK 90 mg arm compared with 33.7% (66/196) of placebo patients. At 52 weeks, the mean improvement from baseline in the SF-36 MCS scores was 4.09 points for subjects treated with USK 45 mg and 4.82 points for those who received USK 90 mg injections.

With respect to health economic assessments, no statistically significant difference was observed in the time lost from work (in days) between the USK treatment groups and control arm at Week 24 for subjects < 65 years old and employed full-time. Similarly, no consistent statistically significant difference between USK treatment and placebo was recorded in the measure of employability due to PsA. Subjects were also asked to indicate how much their disease affected their daily productivity at work, school, or home in the preceding 4 weeks using a 0 to 10 cm VAS scale ('not at all affected' to 'affected very much'). At Week 24, the impact of

PsA on improved productivity was statistically greater in the USK 45 mg group (p = 0.002) and the USK 90 mg arm (p < 0.001) compared with the placebo group. The median change from baseline to Week 24 in self-reported productivity was - 1.30 in the USK 45 mg group, - 2.50 in the USK 90 mg arm compared with - 0.30 in the placebo group.

At Week 52, the mean time lost from work by subjects during the preceding 4 weeks was 0.43 days in the USK 45 mg group and 0.21 days in the USK 90 mg arm. Of the subjects who were unemployable at baseline because of their disease, very few of those patients remained unemployed at Week 52 because of their PsA: 0.8% (1/133) treated with USK 45 mg injections and 1.6% (2/133) given USK 90 mg. With respect to productivity measures taken at Week 52, the median change from baseline was - 1.70 in the USK 45 mg group and - 2.80 in the USK 90 mg arm.

7.1.1.2. Study CNTO1275PSA3002 (PSUMMIT II Study)

7.1.1.2.1. Study design, objectives, locations and dates

The PSUMMIT II trial was a Phase III , randomised, double-blind, placebo-controlled study evaluating the effect of USK in adult subjects with active PsA for at least 6 months despite previous or current treatment with NSAID and/or DMARD. In this study's protocol, at least 150 but not more than 180 of the intended 300 recruited subjects could have been previously treated with single or multiple anti-TNF therapies (defined as 8 weeks of continuous treatment with SC anti-TNF drugs; or 14 weeks of continuous therapy with IV infliximab; or less if the patient was intolerant of anti-TNF therapy). MTX use at a dose ≤ 25 mg/week was allowed during the study, but was not mandatory. No other DMARD use was permitted during the trial.

The primary efficacy objective of the PSUMMIT II Study was to demonstrate the efficacy of USK (given by SC injection at the dose of 45 mg q12w or 90 mg q12w after loading doses at Weeks 0 and 4) on the signs and symptoms of active PsA at 24 weeks, including those patients previously treated with anti-TNF drugs. The secondary efficacy objectives of the study included the assessment of the effects of USK upon functional indices, structural damage, health related QOL and psoriatic skin disease (at 24 and 52 weeks). The study was conducted at 71 sites in 10 countries in Europe and North America: USA (24 sites), Canada (11 sites), United Kingdom (9 sites), Germany (6 sites), Poland (5 sites), Sweden and France (4 sites each), Hungary and Russia (3 sites each), and Austria (2 sites). In the PSUMMIT II Study, the first subject was enrolled on 26 February 2010, and the last subject procedure for this efficacy dataset occurred on 15 November 2012.

The PSUMMIT II Study had a screening phase of up to 6 weeks. At baseline, 300 subjects were planned to be randomly assigned 1:1:1 to receive treatment with USK 45 mg, USK 90 mg, or placebo injections at Weeks 0 and 4 followed by q12w dosing thereafter. During the 24-week placebo-controlled period, assessments were scheduled to occur every 4 weeks. Patients randomised to placebo therapy initially, were crossed-over to active treatment with USK 45 mg injections at Weeks 24 and 28, followed by q12w dosing thereafter. For USK treated subjects (45 and 90 mg groups), placebo injections were given at Weeks 20 and 24 to maintain blinding over the first 24 weeks of the study follow-up. The last dose of study medication was to be administered at Week 40, and subjects were to be followed for efficacy up to Week 52 and for safety up to Week 60. Database locks were scheduled to occur at Weeks 24, 52 and 60. This submission includes the study report up to Week 60 (Week 52 for efficacy outcomes). The trial schema for the PSUMMIT II Study (up to Week 60) is presented in Figure 3.

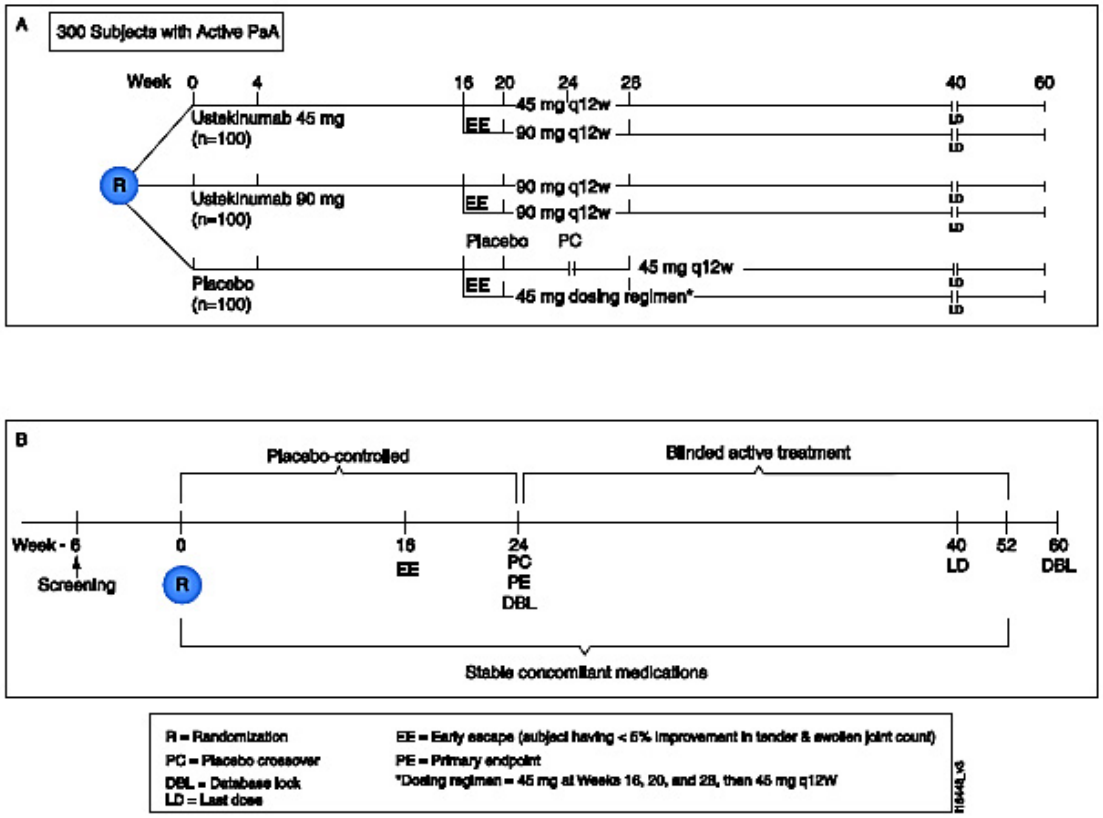
The PSUMMIT II Study had an identical design to the PSUMMIT I trial, including an allowance for early escape in patients failing to improve by Week 16. The main design differences between the PSUMMIT studies were:

- The planned sample size was smaller in PSUMMIT II (n = 300) compared to the PSUMMMIT I (n = 600)

- The duration of the PSUMMIT II Study is shorter (60 weeks) versus 108 weeks in PSUMMIT I, and
- The initial protocol for PSUMMIT II required all subjects to have been previously treated with anti-TNF drugs but the protocol was subsequently amended to include subjects' naïve to anti-TNF therapy. In the PSUMMIT I Study all subjects were to be naïve to anti-TNF drugs.

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 without re-randomisation. All of the placebo escape patients received USK 45 mg at Weeks 16, 20 and 28 followed by 45 mg q12w thereafter, with the last dose to be given at Week 40. For those subjects in the USK 45 mg cohort who qualified for early escape therapy, USK 90 mg was commenced at Week 16, followed by 90 mg q12w thereafter (last dose at Week 40). Subjects in the USK 90 mg treatment group who qualified for escape treatment at Week 16, continued with USK 90 mg injections for the duration of their participation in the study.

Figure 3: Schema for PUMMIT II Study – Up to Week 60.



There were 4 amendments to the original protocol. The first amendment was instituted before the commencement of patient enrolment, and all of the other amendments occurred after. The amendments contained clarifications about baseline assessments, efficacy measures and minor safety related issues. Three of the changes implemented with amendment 3 (27 October 2010) are noteworthy. The screening CRP criterion of ≥ 0.6 mg/dL was decreased to ≥ 0.3 mg/dL. The sponsor states the lower qualifying CRP value is more reflective of the PsA population. Secondly, the inhibition of structural damage objective/endpoint was moved from a co-primary objective/endpoint to a major secondary objective/endpoint. The corresponding information about the power calculation and sample size determination for the structural change endpoint was removed from the protocol. Thirdly, to facilitate enrolment, the study population was broadened to include patients who were naïve to anti-TNF therapy. The change stipulated that at least 180, but no more than 180 of the 300 randomised subjects had to be previously treated

with anti-TNF drugs. These 3 amendments have the potential to have impacted on the integrity of the study's outcomes.

7.1.1.2.2. Inclusion and exclusion criteria

The patient inclusion and exclusion criteria for the PSUMMIT II Study was similar to the PSUMMIT I trial. Adult patients with PsA as per the CASPAR criteria for at least 6 months were eligible for inclusion if they had active disease (defined as ≥ 5/66 swollen and ≥ 5/68 tender joints at screening and baseline; as well as screening CRP ≥ 6.0 mg/L [modified to ≥ 3.0 mg/L after study start] and active or documented history of plaque psoriasis. At baseline, the PSA had to be active despite at least 3 months of DMARD therapy, ≥ 4 weeks of NSAID and/or prior anti-TNF therapy (later amended to 150 - 180/300 recruited patients). A history of active Tuberculosis (TB) was an exclusion criterion, but patients with latent TB (current or past history) were eligible for inclusion if initiated on appropriate prophylaxis. Prohibited recent or past therapies were the same in the PSUMMIT II Study as those listed for the PSUMMIT I trial.

7.1.1.2.3. Study treatments

Subjects were randomised in a 1:1:1 ratio to receive USK 45 mg, USK 90 mg, or placebo injections. USK was supplied in single use, pre-filled syringes with a 27-gauge, 1/2-inch fixed needle. There were 2 dose strengths (that is, 90 mg in 1 mL nominal volume or 45 mg in 0.5 mL nominal volume). Placebo injections were supplied in an identical presentation. At the study site, the pre-filled syringes of USK solution were stored in a secured refrigerator at 2°C to 8°C and were protected from light. There is no comment in the study report about how differences in viscosity between USK and placebo injections may have affected blinding. All injections were given by SC injection into the lateral abdominal wall or upper outer thigh. During each dosing visit where 2 injections were administered, 2 different anatomical sites were injected. During the double-blind phase of the trial, study treatments (including placebo injections) were administered by trained study centre personnel and patients did not self-administer therapy.

Concomitant MTX was allowed during the study if commenced at least 3 months previously and at a stable dose of ≤ 25 mg/week for at least 4 weeks prior to baseline. No conventional DMARD other than MTX was allowed during the trial. Concurrent NSAID and oral CS (≤ 10 mg/day of prednisolone) were permitted if stable for at least 2 weeks prior to baseline. Allowed concomitant medications were to remain stable through to Week 52.

7.1.1.2.4. Efficacy variables and outcomes

The main efficacy variables in the PSUMMIT II Study were identical to the PSUMMIT I trial, and included:

- American College of Rheumatology (ACR) response criteria,
- Disability Index of the HAQ (Health Assessment Questionnaire),
- Psoriasis Area and Severity Index (PASI), and
- Radiographic Response – assessed by the change from baseline over time in the modified van der Heijde-Sharp (vdH-S) score.

The primary efficacy outcome in the PSUMMIT II Study was the rate of ACR20 response at Week 24.

The major secondary efficacy outcomes (all assessed at Week 24) in the order of statistical testing were:

- Change from baseline in the HAQ-DI score,
- Proportion of subjects (with baseline ≥ 3% body surface area [BSA] psoriatic involvement) who achieve a PASI 75 response

- Proportion of subjects with ACR50 response
- Proportion of subjects with ACR70 response, and
- Mean change from baseline in the total vdH-S score. The radiographic data collected in the PSUMMIT I and II studies were pooled for analysis, and will be presented in section 7.1.3 of this report (Week 24 and 52 results).

There were several non-key secondary efficacy outcomes assessed at Weeks 24 and 52, which included: proportion of patients achieving ACR20/50/70; proportion of subjects with HAQ-DI response; percentage change from baseline in enthesitis and dactylitis scores; proportion of patients achieving PsARC response, DAS28 remission (using CRP), and BASDAI response; proportion of subjects with PASI90 and PASI100 responses, and change from baseline in SF-36 scores as well as DLQI, and health economics.

7.1.1.2.5. Randomisation and blinding methods

Subject randomisation at baseline was stratified by 3 factors: investigational site, baseline weight (≤ 100 kg or > 100 kg) and baseline MTX use (yes/no). The randomisation method was minimisation with a biased-coin assignment in a 1:1:1 ratio (USK 45 mg, USK 90 mg, or placebo), resulting in approximately 100 subjects in each treatment group. Randomisation was implemented using dynamic central randomisation with IVRS. Blinding strategies in the PSUMMIT II Study were identical to those used in the PSUMMIT I trial.

7.1.1.2.6. Analysis populations

All of the analyses of efficacy variables were performed using the randomised set of patients, which consisted of all subjects randomised into the trial, analysed by imputation of missing values if required.

7.1.1.2.7. Sample size

The study was powered to detect significant treatment differences in reducing the signs and symptoms of PsA. 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 ACR20 response at Week 24 using a CMH test with stratification by subjects' baseline MTX usage (yes/no). The study had over 99% power to detect the treatment differences ($\alpha = 0.05$) in ACR20 response for at least 1 USK group compared with the control arm, assuming an effect size of 20% to 25% for subjects not receiving MTX and 25% to 30% for subjects receiving MTX, in achieving ACR20 response at Week 24. These assumptions were based on the data from the Phase II PsA study, C0743T10.

7.1.1.2.8. Statistical methods

The PSUMMIT II Study used an identical statistical plan to that of the PSUMMIT I Study – see above for details of PSUMMIT I.

7.1.1.2.9. Participant flow

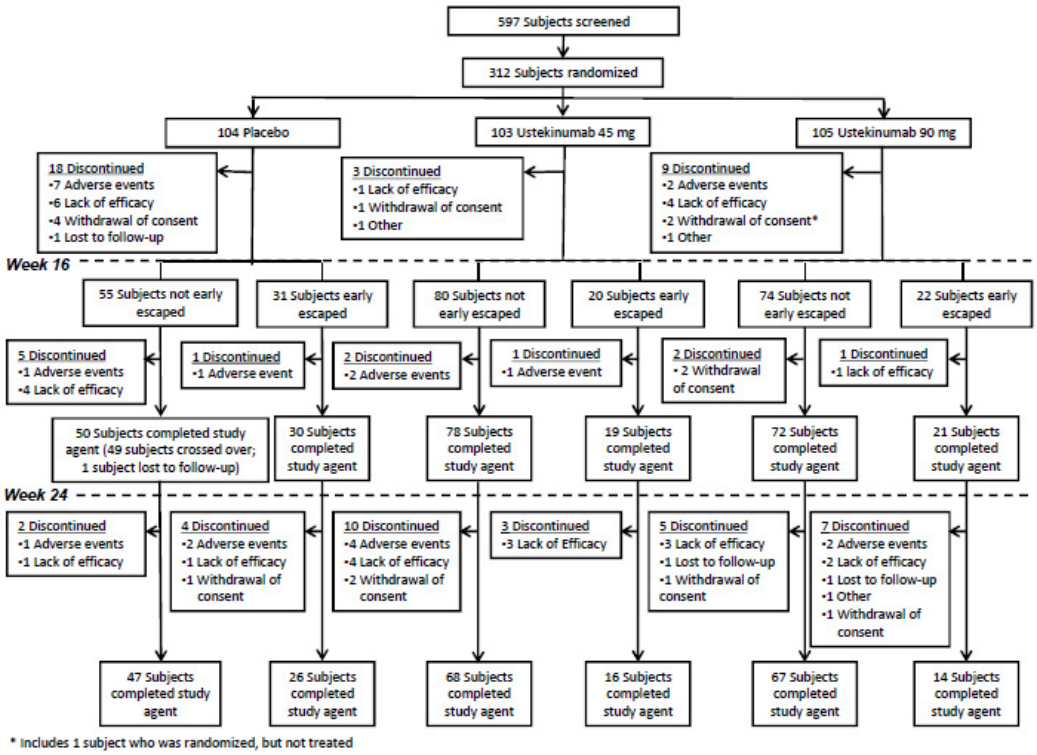
A total of 597 patients were screened for enrolment in the PSUMMIT II Study, and 312 of these subjects were randomised to treatment at Week 0 (103 to the USK 45 mg group, 105 to the USK 90 mg arm, and 104 to placebo). All randomised subjects received their assigned treatment at Week 0 with the exception of 1 subject in the USK 90 mg group who withdrew consent and was never treated.

At Week 16, 31 of 104 (29.8%) subjects in the placebo group met the early escape criteria, and were switched to USK 45 mg injections; and 20 of 103 (19.4%) subjects randomised to USK 45 mg met the early escape criteria and began receiving USK 90 mg injections. Twenty-two of 104 (21.2%) subjects randomised to USK 90 mg qualified for escape, but as per the study protocol all continued to receive treatment with USK 90 mg injections until Week 24 – refer to Figure 4.

At Week 24, a total of 41 (13.1% of 312) subjects in the study had discontinued with a much higher rate of withdrawal in the placebo group (23.1%; 24/104) than the USK 45 mg (5.8%; 6/103) and USK 90 mg (10.5%; 11/105) arms. The most common reason for discontinuation of study medication across all 3 treatment groups by Week 24 was lack of efficacy (4.8%; 15/312) followed by AEs (4.5%; 14/312). Many of the patients who withdrew due to lack of efficacy did so at or before 12 weeks of treatment (6 in the placebo arm, 1 in the USK 45 mg group and 3 in the USK 90 mg arm), which for the USK treated subjects is prior to estimated peak drug effect at 20 - 24 weeks of therapy. The rates of discontinuation at both 16 and 24 weeks were higher in all 3 treatment groups for the subgroup of subjects who were anti-TNF experienced, mainly for lack of efficacy reasons.

A total of 238 subjects (76.3% of 312) completed 52 weeks of treatment follow-up in the PSUMMIT II Study. Of the 74 patients who discontinued study medication before 52 weeks, a higher proportion of those in the placebo group (29.8%; 31/104) did so, compared to the USK treatment arms (18.5% [19/103] in the 45 mg group and 22.9% [24/105] in the 90 mg arm. Lack of efficacy was the most common reason for discontinuation in all of the treatment groups.

Figure 4: Subject Disposition in PSUMMIT II Study through to Week 52.



7.1.1.2.10. Major protocol violations/deviations

Of the 312 patients who were randomised into the PSUMMIT II Study, 21 (6.7%) were recorded as having potentially significant protocol deviations by Week 24: 7.8% (8/103) in the USK 45 mg group, 3.8% (4/105) in the USK 90 mg arm and 8.7% (9/104) in the placebo group. The most common types of protocol deviations were similar in type and incidence for each of the treatment groups, and related to selection criteria not being met (5.4%; 17/312) and missed study drug administration (1.3%; 4/312).

7.1.1.2.11. Baseline data

The treatment groups were well balanced with respect to demographic characteristics. Overall, subjects had a median age of 49 years (range: 19 - 75 years), just over half (52.6%; 164/312) were female, and the majority (98.4%; 307/312) were of Caucasian ethnicity. The overall median BMI was 30.3 kg/m^2 and the majority of subjects (70.8%; 221/312) had a baseline

weight of ≤ 100 kg (median weight 88 kg). By geographic region, the largest percentage of patients came from Europe (53.8%; 167/312) compared to North America (46.2%; 145/312).

The treatment groups were similar with respect to baseline PsA features. The mean duration of PsA for all subjects was 7.98 years (median 5.08 years, range: 0.4 - 57.6 years). A shorter median duration of PsA was observed in the USK 90 mg group (4.49 years) compared to the placebo (5.46 years) and USK 45 mg arms (5.27 years). The median duration of psoriasis was substantially longer in all of the treatment groups (overall 15.12 years). Regarding PsA subtype (as defined by the investigator) recorded at baseline, the majority of patients had either polyarticular arthritis (41.3%; 129/312), asymmetric peripheral arthritis affected (22.8%; 71/312) or spondylitis with peripheral arthritis (22.4%; 70/312). A higher proportion of placebo patients (48.1%; 50/104) had polyarticular arthritis compared to the combined USK cohort (38.0%; 79/208). Isolated DIP joint arthritis was uncommon (13.1%; 41/312) and arthritis mutilans was rare (0.3%; 1/312 – 1 patient in the USK 45 mg group). The majority of patients (70.8%; 221/312) had evidence of enthesitis at baseline, and 40.7% (127/312) had current dactylitis. The incidence of patients suffering enthesitis and dactylitis at baseline in the PSUMMIT II Study is considerably higher than that recorded in the anti-TNF drug trials in subjects with active PsA. All of these disease manifestations occurred at a similar incidence across the treatment groups.

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were similar for the placebo (23.28 and 13.53, respectively) and USK 90 mg (25.87 and 13.95, respectively) groups, but slightly higher in the USK 45 mg arm (27.17 and 14.99, respectively) – refer to Table 10. Similarly, the median HAQ-DI score was higher in the USK 45 mg group (1.38) compared to the other 2 treatment groups (1.25 for both placebo and the USK 90 mg arm). Overall, the HAQ-DI scores are consistent with moderately severe disease activity. The mean CRP for subjects in the USK 45 mg group was higher at 26.62 mg/L compared to the USK 90 mg arm (20.21 mg/L) and control (15.85 mg/L).

Table 10: Baseline Activity of Psoriatic Arthritis in PSUMMIT II Study (Randomised Subjects).

		Ustekinumab			
	Placebo	45 mg	90 mg	Combined	Total
Subjects randomized	104	103	105	208	312
Number of swollen joints (0-66)					
N	104	103	105	208	312
Mean (SD)	13.53 (9.853)	14.99 (9.248)	13.95 (10.898)	14.47 (10.104)	14.15 (10.015)
Median	11.00	12.00	11.00	12.00	11.00
IQ range	(7.00; 18.00)	(8.00; 19.00)	(7.00; 17.00)	(7.00; 18.00)	(7.00; 18.00)
Range	(3.0; 61.0)	(5.0; 59.0)	(4.0; 61.0)	(4.0; 61.0)	(3.0; 61.0)
Number of tender joints (0-68)					
N	104	103	105	208	312
Mean (SD)	23.38 (14.898)	27.17 (15.400)	25.87 (15.533)	26.51 (15.444)	25.47 (15.312)
Median	21.00	22.00	22.00	22.00	22.00
IQ range	(11.00; 30.00)	(15.00; 33.00)	(14.00; 36.00)	(15.00; 35.50)	(14.00; 33.00)
Range	(4.0; 68.0)	(7.0; 66.0)	(5.0; 68.0)	(5.0; 68.0)	(4.0; 68.0)
Patient's assessment of pain (VAS; 0-10 cm)					
N	104	103	105	208	312
Mean (SD)	6.42 (2.000)	6.77 (1.945)	6.56 (1.986)	6.66 (1.964)	6.58 (1.976)
Median	6.55	6.90	6.80	6.90	6.80
IQ range	(5.10; 7.85)	(5.60; 8.40)	(5.20; 8.10)	(5.40; 8.25)	(5.20; 8.10)
Range	(1.4; 10.0)	(1.2; 9.9)	(0.7; 9.9)	(0.7; 9.9)	(0.7; 10.0)
Patient's global assessment of disease activity (VAS; 0-10 cm)					
N	104	103	105	208	312
Mean (SD)	5.87 (1.669)	6.10 (2.042)	6.13 (1.913)	6.11 (1.973)	6.03 (1.878)
Median	6.10	6.40	6.30	6.40	6.20
IQ range	(4.75; 7.00)	(4.50; 7.60)	(5.00; 7.70)	(4.85; 7.65)	(4.80; 7.50)
Range	(1.6; 9.2)	(1.1; 9.9)	(1.1; 9.9)	(1.1; 9.9)	(1.1; 9.9)
Physician's global assessment of disease activity (VAS 0-10 cm)					
N	104	103	105	208	312
Mean (SD)	6.59 (1.925)	6.81 (1.908)	6.68 (1.846)	6.74 (1.874)	6.69 (1.889)
Median	7.10	7.20	7.00	7.05	7.10
IQ range	(5.25; 7.95)	(5.80; 8.30)	(5.40; 7.90)	(5.60; 8.10)	(5.40; 8.05)
Range	(1.2; 9.9)	(1.3; 9.9)	(1.3; 10.0)	(1.3; 10.0)	(1.2; 10.0)
HAQ-DI score (0-3)					
N	104	103	104	207	311
Mean (SD)	1.25 (0.723)	1.34 (0.704)	1.29 (0.666)	1.31 (0.684)	1.29 (0.697)
Median	1.25	1.38	1.25	1.38	1.25
IQ range	(0.75; 1.81)	(0.75; 1.88)	(0.75; 1.88)	(0.75; 1.88)	(0.75; 1.88)
Range	(0.0; 2.9)	(0.0; 2.9)	(0.0; 2.8)	(0.0; 2.9)	(0.0; 2.9)
CRP (mg/L)					
N	104	103	105	208	312
Mean (SD)	15.85 (19.737)	26.62 (35.388)	20.21 (30.592)	23.38 (33.130)	20.87 (29.533)
Median	8.53	13.00	10.10	10.20	9.32
IQ range	(4.58; 21.95)	(4.54; 36.30)	(4.83; 19.80)	(4.69; 27.15)	(4.61; 24.00)
Range	(0.6; 139.0)	(0.3; 182.0)	(0.5; 196.0)	(0.3; 196.0)	(0.3; 196.0)

Overall, the majority of subjects (86.2%; 269/312) had received previous DMARD treatment, and the pattern of prior DMARD use was similar in each of the treatment groups. Most subjects (74.4%; 232/312) had prior use of only 1-2 DMARDs, but 11.9% (37/312) had experienced > 2 previous DMARDs. The 3 most commonly used prior DMARDs were MTX (83.8%; 260/312), SSZ (26.3%; 82/312) and LEF (14.4%; 45/312).

The majority of patients (84.8%; 263/312) in all treatment groups had a past history of taking NSAIDs, and just over a third (36.9%; 114/312) of subjects had previously taken low dose oral CS.

In total, 180 patients had a prior history of receiving anti-TNF drugs: 59.6% (62/104) in the placebo group, 56.3% (58/103) in the USK 45 mg arm, and 57.1% (60/105) in the USK 90 mg group. The trial protocol allowed for TNF experienced subjects to have had exposure to up to 5 different agents, and more than 50% of those subjects had prior use of 2 or more anti-TNF drugs, reflecting a highly treatment refractory PsA population. Approximately half of the TNF experienced patients had taken such drugs for at least 12 months, and the most common reason for discontinuation of anti-TNF therapy in the past was lack of efficacy (68%). The 3 most commonly used prior anti-TNF drugs were etanercept (36.9%; 115/312), adalimumab (32.4%; 101/312) and infliximab (30.8%; 96/312). A small proportion of subjects had tried golimumab (5.1%; 16/312) and 3 subjects had experienced certolizumab (1.0%). Three subjects also had prior exposure to anakinra (1 placebo subject and 2 patients in the USK 90 mg group). The rates of previous and concurrent MTX, NSAID and CS were similar between the TNF experienced versus TNF naïve patient subsets.

During the PSUMMIT II Study, almost half of all subjects (49.7%; 155/312) continued MTX therapy. Use of concomitant MTX was slightly higher in the USK treated patients (52.4% [54/103] in the 45 mg group and 49.5% [52/105] in the 90 mg arm) compared to the placebo

group (47.1%; 49/104). The mean and median weekly dose of concurrent MTX used in all 3 groups was similar: placebo 17.4/17.5 mg, USK 45 mg 17.2/15.0 mg and USK 90 mg 15.9/15.0 mg. In addition, the majority of patients (70.2%; 219/312) in all treatment groups took concomitant NSAID during the trial, and approximately one sixth (16.0%; 50/312) of subjects took low dose oral CS (median daily dose of 7.5 mg in the USK 90 mg and placebo groups, but 5.0 mg in the USK 45 mg arm).

Regarding concurrent skin psoriasis at baseline, the majority of subjects in each of the 3 treatment groups had ≥ 3% BSA psoriasis skin involvement: 76.9% (80/104) in the placebo group, 77.7% (80/103) in the USK 45 mg arm and 77.1% (81/105) in the USK 90 mg group. At baseline, the mean PASI score (with range) was slightly lower in the placebo group (7.9 [4.5-16.0]) compared to the USK 45 mg (8.6 [4.5-18.3]) and the USK 90 mg groups (8.8 [4.5-18.0]). The mean baseline DLQI scores were similar between the treatment groups: 11.0 (5.0-16.5) in the placebo group, 11.0 (6.0-18.0) in the USK 45 mg arm and 10.0 (6.0-18.0) in the USK 90 mg group.

The incidence of relevant comorbid conditions was similar in the treatment groups. Regarding risk factors for cardiovascular disease, a past history of hypertension was recorded in 43.6% of all subjects, 20.8% reported hyperlipidaemia, 13.8% recorded diabetes mellitus and 7.1% had a history of established coronary artery disease. Nearly half of all subjects (47.4%) reported current alcohol consumption (median weekly consumption of 2 standard drinks), and 20.8% were current smokers (median daily cigarette use of 15). Past history of depression was recorded in 21.5% of patients. Hospitalisation in the last 12 months was reported in 19.2% of subjects, including 6.7% of patients having a prior hospitalisation for infection.

7.1.1.2.12. Results for the primary efficacy outcome

At Week 24, a significantly greater proportion of subjects in the combined USK, USK 45 mg, and USK 90 mg groups (43.8% [91/208], 43.7% [45/103], and 43.8% [46/105], respectively) achieved an ACR20 response compared with subjects in the placebo group (20.2%; 21/104). Both p-values by either the re-randomisation test (primary analysis) or the CMH test (sensitivity analysis) were significant ($p < 0.001$) – refer to Table 11. The ACR20 response rate at Week 24 was identical in the 2 USK treatment groups.

Table 11: Number and Proportion of Subjects achieving ACR20 Response at 24 Weeks in PSUMMIT II Study (Randomized Subjects).

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	104	103	105	208
ACR 20				
N	104	103	105	208
Subjects in response	21 (20.2%)	45 (43.7%)	46 (43.8%)	91 (43.8%)
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.

Three sensitivity analyses were conducted to test the robustness of the primary endpoint analysis, and to assess the impact of missing data. All of the sensitivity analyses showed results consistent with the main analysis outcome, thereby supporting the claim that the main analysis results were robust and not impacted by the data handling rules for missing data. One additional analysis was also conducted to assess the impact of early escape when the early escape rules were not implemented. As expected, the ACR20 response rate increased across all 3 treatment groups as compared with the main analysis, particularly in the placebo group, which reflects the early escape of placebo subjects to USK treatment. However, the ACR20 response rate was still statistically significant for subjects in the USK 45 mg (45.6%) and USK 90 mg (49.5%) groups compared with the placebo arm (19.4%) in this sensitivity analysis.

Study site did not affect the number of subjects who achieved an ACR20 response at Week 24. The number of subjects who achieved an ACR20 response by screening date (cut-off of 31 December 2010) was also considered. This cut-off date was chosen to approximate when protocol amendment 3 was implemented (that is, when the screening CRP was lowered from ≥ 0.6 mg/dL to ≥ 0.3 mg/dL). The majority of the subjects (68.3%; 213/312) were enrolled after 31 December 2010. Regardless of enrolment before or after the 31 December 2010, consistently greater proportions of subjects in the USK 45 mg and 90 mg groups achieved ACR20 response at Week 24; however, the ACR20 response rates at Week 24 were higher across all 3 treatment groups among subjects enrolled after 31 December 2010, especially in the placebo group. This could be explained by the fact that the ACR20 response rates were generally lower (for all treatment groups) in the patients with prior TNF exposure versus the later expanded patient recruitment criteria with a mixture of TNF experienced and naïve subjects.

Randomisation was stratified by MTX use at baseline, and the 24-week ACR20 response rates observed in subjects receiving MTX at baseline versus those not receiving MTX at baseline were similar for the USK treatment groups. However, in the placebo group, concurrent MTX users had a higher ACR20 response rate at 24 weeks (28.6%) than those not receiving MTX (12.7%).

Randomisation was also stratified by baseline weight (≤ 100 kg [n = 221] versus > 100 kg [n = 90]). For both USK treatment groups, the 24-week ACR20 response rate was similar in both weight categories: 43.2% in the 45 mg group and 46.6% in the 90 mg arm for subjects weighing ≤ 100 kg (23.0% response rate in placebo) versus 44.8% in the 45 mg group and 38.7% in the 90 mg arm for subjects weighing > 100 kg (13.3% response rate in placebo group). However, for the higher levels of ACR response (50 and 70), a greater proportion (2-fold or greater) of USK treated patients weighing ≤ 100 kg achieved the endpoint versus those weighing > 100 kg:

- ACR50 ≤ 100 kg cohort: 20.3% in the USK 45 mg group and 28.8% in the USK 90 mg arm (versus 8.1% for placebo)
- ACR50 > 100 kg cohort: 10.3% in the USK 45 mg group and 9.7% in the USK 90 mg arm (versus 3.3% for placebo)
- ACR70 ≤ 100 kg cohort: 8.1% in the USK 45 mg group and 11.0% in the USK 90 mg arm (versus 4.1% for placebo)
- ACR70 > 100 kg cohort: 3.4% in the USK 45 mg group and 3.2% in the USK 90 mg arm (versus 0% for placebo)

A total of 180 subjects were anti-TNF experienced (62 in the placebo group, 60 in the USK 45 mg arm and 58 in the USK 90 mg group) in the PSUMMIT II Study and the rate ACR20 response at Week 24 was also analysed by prior anti-TNF exposure or naïve. For all 3 treatment groups the rate of ACR20 response was lower in the anti-TNF experienced versus naïve cohorts: 14.5% (9/62) and 28.6% (12/42) respectively for the placebo group, 36.7% (22/60) and 53.5% (23/43) respectively for the USK 45 mg arm and 34.5% (20/58) and 55.3% (26/47) respectively for the USK 90 mg group. Furthermore, when ACR20 response at Week 24 was analysed by the number of previous anti-TNF drug, the response rate was higher in those with exposure to only 1 anti-TNF medicine (n = 81) or 2 (n = 54) compared with those who had used 3 or more (n = 45). For the subset of patients who had used 3 or more anti-TNF drugs previously, the rate of ACR20 response at 24 weeks between USK treatment and placebo showed little difference. Unexpectedly, the reason for discontinuation of anti-TNF (lack of efficacy versus intolerance) did not appear to influence the ACR20 response rate at 24 weeks.

7.1.1.2.13. Results for other efficacy outcomes

7.1.1.2.13.1. Change from baseline to week 24 in HAQ-DI score

Significantly greater improvements from baseline to Week 24 in HAQ-DI scores were observed in subjects in the combined USK (median change from baseline of - 0.25) cohort, as well as the individual USK 45 mg and 90 mg groups compared with subjects in the placebo group (median

change of 0). All of the pair-wise comparisons of active treatment versus placebo, by either the re-randomisation test or the test of analysis on the van der Waerden normal scores (sensitivity analysis) were statistically significant ($p < 0.001$) – refer to Table 12. The mean improvement in HAQ-DI score at Week 24 was numerically higher in the USK 90 mg group (- 0.25) compared with the USK 45 mg group (- 0.13) but no formal statistical comparison was provided.

Table 12: Summary of Change from Baseline in HAQ-DI Score at Week 24 in PSUMMIT II Study.

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	104	103	105	208
Change from baseline				
N	104	103	105	208
Mean (SD)	-0.03 (0.380)	-0.21 (0.461)	-0.22 (0.436)	-0.21 (0.447)
Median	0.00	-0.13	-0.25	-0.25
IQ range	(-0.13; 0.13)	(-0.38; 0.00)	(-0.50; 0.00)	(-0.38; 0.00)
Range	(-1.3; 1.0)	(-1.8; 1.0)	(-1.9; 1.5)	(-1.9; 1.5)
p-value[a]		0.001	< 0.001	< 0.001
p-value[b]		0.002	< 0.001	< 0.001

[a] Based on the test of analysis of covariance on the van der Waerden normal scores.
[b] Based on re-randomization test.

7.1.1.2.13.2. PASI 75 response at week 24

At 24 weeks, a significantly greater proportion of subjects with ≥ 3% BSA psoriasis skin involvement at baseline in the combined, 45 mg and 90 mg USK groups (53.4% [86/161], 51.3% [41/80] and 55.6% [45/81], respectively) achieved a PASI 75 response compared with subjects in the placebo group (5.0%; 4/80). All p-values for the pair-wise comparison of USK versus placebo were statistically significant ($p < 0.001$) – refer to Table 13. A numerically higher rate of PASI 75 response at Week 24 was observed in the USK 90 mg group (55.6%) compared with the USK 45 mg arm (51.3%). Like the ACR20 response rates at Week 24, prior anti-TNF exposure predicted a lower likelihood of achieving PASI 75 response, regardless of treatment.

Table 13: Number of Subjects achieving PASI 75 Response at 24 Weeks in PSUMMIT II Study (Randomized Subjects with ≥ 3% BSA skin psoriasis involvement at baseline).

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Randomized subjects with ≥ 3% BSA psoriasis skin involvement at baseline	80	80	81	161
PASI 75				
N	80	80	81	161
Subjects in response	4 (5.0%)	41 (51.3%)	45 (55.6%)	86 (53.4%)
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.

7.1.1.2.13.3. ACR50 and ACR70 response rates at week 24

At Week 24, a significantly greater proportion of subjects in the combined USK group and in each of the individual USK groups achieved either an ACR50 or ACR70 response compared with the placebo group – refer to Table 14. P-values by either the re-randomisation test or the CMH chi-square test (sensitivity analysis) were statistically significant in favour of USK versus placebo. The ACR50 and ACR70 responses at 24 weeks were numerically higher in the USK 90 mg group compared with the USK 45 mg treated arm. For the subjects treated with USK (either dose) the use of concurrent (yes/no) did not have an effect on the rate of ACR50 and ACR70 response at 24 weeks. However, subject weight did appear to influence the rate of ACR50 and ACR70 response for all treatment groups (including the control arm). Published evidence confirms that obesity is associated with reduced disease control in inflammatory arthritis, including PsA. For the combined USK cohort the rate of ACR50 response at Week 24 in those weighing ≤ 100 kg was 24.5% versus 10.0% for those weighing > 100 kg (placebo 8.1% if

weighing ≤ 100 kg and 3.3% for those weighing > 100 kg). Similarly, for the combined USK cohort the rate of ACR70 response at Week 24 in those weighing ≤ 100 kg was 9.5% versus 3.3% for those weighing > 100 kg (placebo 4.1% if weighing ≤ 100 kg and 0% for those weighing > 100 kg).

Table 14: Number of Subjects achieving ACR50 and ACR70 Response at 24 Weeks in PSUMMIT II Study (Randomized Subjects).

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	104	103	105	208
ACR 50				
N	104	103	105	208
Subjects in response	7 (6.7%)	18 (17.5%)	24 (22.9%)	42 (20.2%)
p-value[a]		0.018	0.001	0.002
p-value[b]		0.018	< 0.001	0.002
ACR 70				
N	104	103	105	208
Subjects in response	3 (2.9%)	7 (6.8%)	9 (8.6%)	16 (7.7%)
p-value[a]		0.190	0.078	0.095
p-value[b]		0.171	0.060	0.094

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

7.1.1.2.14. Other efficacy outcomes

7.1.1.2.14.1. ACR20/50/70 response rates at week 52

At Week 52, the proportion of subjects treated with USK (either dose) achieving an ACR20/50/70 response was maintained to that observed at Week 24. For those receiving USK 45 mg, the rate of ACR20 response at 52 weeks was 46.8% (44/94), ACR50 response was 27.7% (26/94) and the ACR70 response rate was 12.8% (12/94). For those subjects assigned to the USK 90 mg group, the rate of ACR20 response at 52 weeks was 48.4% (46/95), ACR50 response was 26.3% (25/95) and the ACR70 response rate was 17.9% (17/95).

At Week 24, patients in the placebo group were commenced on USK 45 mg injections, and their rate of ACR response at 52 weeks significantly increased compared to that observed at Week 24. For the subjects in the placebo to USK 45 mg cohort, the rate of ACR20 response at 52 weeks was 55.8% (43/77), ACR50 response was 28.6% (22/77) and the ACR70 response rate was 15.6% (12/77).

For patients treated with USK at entry, ACR responses at Week 52 were also analysed by subject weight at baseline (> 100 kg versus ≤ 100 kg). For subjects weighing ≤ 100 kg (n = 147), ACR response rates are similar regardless of whether USK 45 mg or 90 mg injections are used – refer to Table 15. For subjects weighing > 100 kg (n = 60), the various levels of ACR response were similar for both USK doses but significantly lower compared to subjects weighing ≤ 100 kg. Concomitant MTX use did not appear to affect the rates of ACR response in either of the USK treatment groups; however, these results should be cautiously interpreted, as the use of MTX was not randomly assigned.

Table 15: ACR Response Rates at 52 Weeks in PSUMMIT II Study (Randomized Subjects stratified according to subject weight at baseline).

	Randomized subjects with weight ≤100 kg at baseline		Randomized subjects with weight >100 kg at baseline	
	Ustekinumab			
	45 mg	90 mg	45 mg	90 mg
Number of subjects	74	73	29	31
Subjects in response				
N	67	67	27	28
ACR 20	33 (49.3%)	36 (53.7%)	11 (40.7%)	10 (35.7%)
ACR 50	21 (31.3%)	20 (29.9%)	5 (18.5%)	5 (17.9%)
ACR 70	10 (14.9%)	15 (22.4%)	2 (7.4%)	2 (7.1%)

Abbreviation: N=sample size.

7.1.1.2.14.2. HAQ response over time

At Week 24, a higher proportion of subjects treated with USK achieved a clinically meaningful (≥0.3) improvement in their HAQ-DI score from baseline than those in the placebo group (34.0% [35/103] in the USK 45 mg group and 38.1% [40/105] in the USK 90 mg arm versus 16.3% [17/104] in the placebo arm; p-value < 0.001 for the pair-wise comparison of placebo to the combined USK cohort as well as each individual USK dose group). At Week 52, the proportion of HAQ responders in USK treated subjects progressively declined with time after Weeks 28 in the USK 45 mg group (41.4% at 28 weeks and 35.1% at 52 weeks) but was maintained over extended time in the USK 90 mg arm (47.5% at 28 weeks and 44.2% at 52 weeks). After initiation of USK 45 mg in the placebo group the proportion of HAQ responders at 52 weeks was 37.7%.

At Week 52, the median change from baseline in the HAQ-DI score was - 0.25 in both the USK 45 mg and 90 mg groups. After initiation of USK 45 mg injections at Week 24, the median change from baseline in the HAQ-DI score for those in the original placebo group was - 0.06 at Week 52, and - 0.13 in those switched at Week 16 because of meeting the early escape criteria.

7.1.1.2.14.3. Enthesitis and dactylitis at weeks 24 and 52

At baseline, 70.8% (221/312) of all randomised subjects reported enthesitis. At 24 weeks, the proportion of subjects with documented ongoing enthesitis was statistically lower in the USK 45 mg group (75.7% [53/70]; p < 0.05) and the USK 90 mg arm (70.0% [49/70]; p < 0.05) compared with the placebo group (88.2%; 60/68). Furthermore, for subjects with enthesitis at baseline, significant median percentage improvements at Week 24 in the MASES score were observed for the USK 90 mg arm (median improvement of 48.33% from a baseline score of 5.0; p < 0.008) compared with the placebo group (zero median percentage improvement from a baseline score of 7.0). However, the comparison between the USK 45 mg group for the median percentage improvement in the MASES score (median improvement of 33.33% from a baseline score of 6.0) and placebo was not statistically significant (p = 0.098). No comparison between the USK 90 mg and USK 45 mg groups was presented.

At Week 52, among the subjects with enthesitis at baseline, the percentage of USK treated patients with ongoing documented enthesitis was 75.8% in the 45 mg dose group and 57.7% in the 90 mg arm. In the placebo to USK 45 mg dose switch group, the proportion of subjects with enthesitis at Week 52 was 67.9%. At Week 52, the median percentage improvement in the modified MASES index was 36.7% in the USK 45 mg dose group and 60.0% in the USK 90 mg arm. For the placebo to USK 45 mg dose switch cohort, the median percentage improvement from baseline to Week 52 was 33.33%.

At baseline, 40.7% (127/312) of all randomised subjects recorded at least 1 digit with dactylitis. At Week 24, the proportion of subjects with ongoing dactylitis in 1 or more digits was significantly lower in the USK 90 mg group (57.9% [22/38]) compared with the placebo arm (75.8%; 25/33), but not so for the comparison between control and the USK 45 mg group (65.2%; 30/46). In addition, for subjects with dactylitis at baseline, numerically higher median percentage improvements at Week 24 in the dactylitis score were observed in the USK 90 mg group (median improvement of 64.58% from a baseline score of 7.0) compared with the placebo group (zero median percentage improvement from a baseline score of 7.0), but this comparison did not reach statistical significance (p = 0.166). The USK 45 mg group showed no improvement in dactylitis (zero median percentage improvement from a baseline score of 5.0).

At Week 52, among the subjects with dactylitis at baseline, the percentage of USK treated patients with ongoing documented dactylitis was 50.0% in both dose groups. In the placebo to USK 45 mg dose switch group, the proportion of subjects with dactylitis at Week 52 was 33.3%. At Week 52, the median percentage improvement in the dactylitis score was > 90% in all 3 treatment groups (USK 45 mg and 90 mg arms, as well as the placebo to USK 45 mg dose switch group).

7.1.1.2.14.4. PsARC response rates at weeks 24 and 52

Higher proportions of subjects in the USK treatment groups achieved PsARC response at Week 24 compared with the placebo group, and the response rate was maintained from Week 24 through to Week 52. The proportion of subjects achieving PsARC response at Week 24 was 55.3% (57/103) in the USK 45 mg group and 51.4% (54/105) in the USK 90 mg compared to 30.8% (32/104) in the placebo group ($p < 0.05$ for the comparison between each USK dose group and the combined USK cohort versus placebo). At Week 52, the rate of PsARC response was 58.5% in the USK 45 mg group and 60.0% in the USK 90 mg arm. For the placebo to USK 45 mg dose switch group (at Week 24), the rate of PsARC response at 52 weeks was 64.9%.

7.1.1.2.14.5. DAS28 remission rate at weeks 24 and 52

At 24 weeks, a statistically greater proportion of subjects treated with USK 90 mg (15.2%; 16/105) achieved DAS28 remission compared to those treated with placebo injections (3.85% [4/104]; $p < 0.05$). Those in the USK 45 mg dose group achieved a rate of DAS28 remission at 24 weeks (10.7%; 11/103) that was numerically higher than placebo, but not reaching statistical significance.

At Week 52, the proportions of patients in DAS28 remission in the USK 45 mg and 90 mg groups were 18.1% and 21.1%, respectively. After initiation of USK 45 mg at Week 24, the original placebo group showed a similar rate of DAS28 remission (22.1%) at 52 weeks.

7.1.1.2.14.6. BASDAI response rates at week 24

At Week 24, a significantly higher proportion of subjects treated with USK achieved at least a 20% improvement from baseline in their BASDAI score compared with the placebo group. At Week 24, the BASDAI 20 response rate was similar in all 3 treatment groups: 60.0% (15/25) in the USK 45 mg group, 52.4% (11/21) in the USK 90 mg arm and 55.6% (10/18) in the placebo group. However, the BASDAI 50 response rate was statistically higher in the USK 90 mg group (38.1%; 8/21), but not in the USK 45 mg arm (28.0%; 7/25) when compared with the control group (5.6%; 1/18). At Week 24, a higher proportion of subjects treated with USK achieved a BASDAI 70 response: 12.0% (3/25) in the USK 45 mg group and 23.8% (5/21) in the USK 90 mg arm compared with no subjects in the placebo group achieving this level of response, but the p-vale for USK versus control was not estimated.

7.1.1.2.14.7. PASI response rates at weeks 24 and 52

In the subset of subjects with ≥ 3% BSA psoriasis skin involvement at baseline, those who received USK (either dose) as compared with the placebo group achieved a significantly higher rate of PASI 90 and 100 responses through by Week 24. The rate of PASI 90 response at 24 weeks was 30.0% (24/80) in the USK 45 mg group and 44.4% (36/81) in the USK 90 mg arm compared with 3.8% (3/80) in the placebo group. The rate of PASI 100 response at 24 weeks was 16.3% (13/80) in the USK 45 mg group and 21.0% (17/81) in the USK 90 mg arm compared with 1.3% (1/80) in the placebo group. In general, higher rates of PASI response were observed in USK treated subjects (either dose) weighing ≤ 100 kg at baseline as opposed to patients weighing > 100 kg at baseline. The use of concurrent MTX (yes/no) had no effect on the rate of PASI response for USK treated subjects.

PASI responses observed at Week 24 were maintained through to Week 52. For example, the proportion of subjects with PASI 75 response at 52 weeks was 56.5% in the USK 45 mg group and 64.4% in the USK 90 mg arm. For patients who switched from placebo to USK 45 mg injections at Week 24, the PASI 75 response rate at 52 weeks was 56.1%.

Another supporting efficacy endpoint was the proportion of subjects who achieved a combination of skin and joint responses (PASI 75 and ACR20 response) at Week 24. A significantly greater proportion of USK treated subjects achieved this dual response (30.0% [24/80] for USK 45 mg and 38.3% [31/81] for USK 90 mg) compared to those in the control arm (2.5% [2/80]; $p < 0.001$ for both comparisons).

7.1.1.2.14.8. Health related QOL outcomes at weeks 24 and 52

In the subset of patients with ≥ 3% BSA psoriasis skin involvement and reporting a DLQI score > 1 at baseline, significantly higher proportions of subjects in the USK treatment groups at Week 24 compared with the placebo arm recorded a DLQI score of 0 or 1 (that is, psoriasis considered to have no effect on the patient's life). At Week 24, the proportion of subjects with a DLQI score of 0 or 1 was 35.6% (28/77) in the USK 45 mg group and 42.6% (32/75) in the USK 90 mg arm compared with 11.1% (8/73) in the placebo group. At Week 52, the percentage of patients with a DLQI score of 0 or 1 was 34.3% in the USK 45 mg group and 46.2% in the USK 90 mg arm. For the placebo to USK 45 mg dose switch group (at Week 24), the proportion of patients with a DLQI score of 0 or 1 at 52 weeks was 37.5%.

At Week 24, the median change from baseline in the SF-36 PCS scores was statistically greater in the USK 90 mg treatment group (3.50 point median improvement from a baseline median of 28.15 [n = 97]) compared with the placebo arm (zero median improvement from a baseline median of 29.35 [n = 97]; $p < 0.01$). The pair-wise comparison between USK 45 mg (2.70 point median improvement from a baseline mean of 27.95 [n = 99]) and placebo was statistically significant ($p < 0.05$). At Week 24, the proportion of subjects that achieved a clinically meaningful improvement (≥ 5 point improvement from baseline in the SF-36 PCS score) was significantly greater in the USK treatment groups compared with the control arm. At Week 24, the proportion of subjects with ≥ 5 point improvement from baseline in SF-36 PCS score was 37.4% (37/99) in the USK 45 mg group and 44.3% (43/97) in the USK 90 mg arm compared with 19.6% in the placebo group (19/97; $p < 0.05$ for both pair-wise comparisons). At 52 weeks, the mean improvement from baseline in the SF-36 PCS scores was 4.76 points for subjects treated with USK 45 mg and 5.91 points for those who received USK 90 mg injections.

At Week 24, the median change from baseline in the SF-36 MCS scores for those who received USK were numerically greater compared to control patients, but did not reach statistical significance. The USK 90 mg group showed a 2.20 median point improvement from a baseline median of 41.40 (n = 97), the USK 45 mg arm demonstrated a 0.70 median point improvement from a baseline median of 43.70 (n = 99), and the placebo group showed a zero median improvement from a baseline median of 41.80 (n = 97). At Week 24, the proportions of subjects that achieved a clinically meaningful cut-off (≥ 5 point improvement from baseline in SF-36 MCS score) were numerically higher and statistically significant in both of the USK treatment groups compared with placebo. At Week 24, the proportion of subjects with ≥ 5 point improvement from baseline in SF-36 MCS score was 37.4% (37/99) in the USK 45 mg group and 44.3% (43/97) of the subjects in the USK 90 mg arm compared with 19.6% (19/97) of placebo patients. At 52 weeks, the mean improvement from baseline in the SF-36 MCS scores was 1.84 points for subjects treated with USK 45 mg and 3.68 points for those who received USK 90 mg injections.

With respect to health economic assessments, a statistically significant difference was observed in the time lost from work (in days) between the USK treatment groups and control arm at Week 24 for subjects < 65 years old and employed full-time. However, no consistent statistically significant difference between USK treatment and placebo was recorded in the measure of employability due to PsA. Subjects were also asked to indicate how much their disease affected their daily productivity at work, school, or home in the preceding 4 weeks using a 0 to 10 cm VAS scale ('not at all affected' to 'affected very much'). At Week 24, the impact of PsA on improved productivity was statistically greater in both USK treatment groups compared with the placebo arm ($p < 0.001$ for both pair-wise comparisons). The median change from baseline to Week 24 in 'self-reported productivity' was - 1.50 in the USK 45 mg group, - 2.20 in the USK 90 mg arm compared with no change in the placebo group.

At Week 52, the mean time lost from work by subjects during the preceding 4 weeks was 1.47 days in the USK 45 mg group and 0.30 days in the USK 90 mg arm. Of the subjects who were unemployable at baseline because of their disease, very few of those patients remained

unemployed at Week 52 because of their PsA: 8.1% (5/62) treated with USK 45 mg injections and 3.5% (2/57) given USK 90 mg. With respect to productivity measures taken at Week 52, the median change from baseline was - 1.77 in the USK 45 mg group and - 2.07 in the USK 90 mg arm.

7.1.2. Other efficacy studies

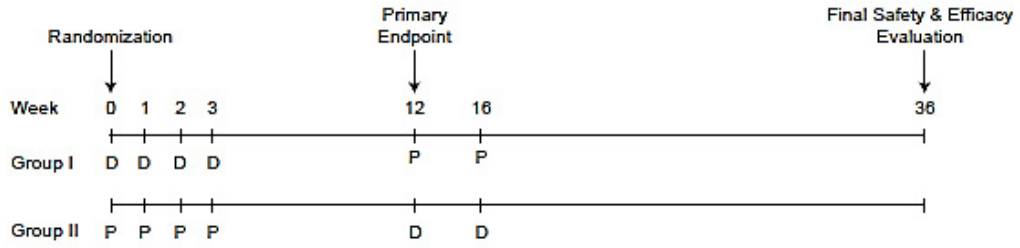
7.1.2.1. Study C0743T10

7.1.2.1.1. Study design and treatments

Study C0743T10 was a Phase II, randomised, double-blind, placebo-controlled study evaluating the effect of USK in adult subjects with active PsA for at least 6 months, who had an inadequate response to standard treatment options (including MTX, CS, NSAID and/or anti-TNF therapies. The primary efficacy objective of the trial was to demonstrate the efficacy of USK given weekly for 4 doses by SC injection at a dose of 90 mg [or 63 mg after filtration] for 4 doses [Weeks 0, 1, 2 and 3] on the signs and symptoms of active PsA at 12 weeks. The secondary efficacy objectives of the study included the assessment of the effects of USK upon health related QOL and psoriatic skin disease. The study was conducted at 24 sites in the USA, Canada (11 sites), Finland, Switzerland and Denmark. The study period was between 21 December 2005 and 20 September 2007.

As illustrated in Figure 5, patients were randomly assigned to 1 of 2 treatment groups. Group I (n = 76) received 4 weekly injections of USK 90 mg at Weeks 0, 1, 2 and 3. The primary efficacy endpoint evaluation was performed at 12 weeks, and Group I subjects received matching placebo injections at Weeks 12 and 16. The final efficacy evaluation was undertaken at 36 weeks. Group II (n = 70) received placebo injections at Weeks 0, 1, 2 and 3; and then crossed over to receive USK at Weeks 12 and 16.

Figure 5: Schema for Study C0743T10 Through to 36 Weeks.



D = USK; P = Placebo

The USK dosing regimen proposed in this study was based on the findings of another Phase II Study (C0379T40) in adult patients with psoriasis. This trial examined 4 weekly SC doses of USK 45 mg or 90 mg, and found that the PASI 75 responses at 12 weeks were 67.2% and 81.3%, respectively. The study also indicated a potential impact of subject weight upon efficacy with the proportion of subjects achieving PASI 75 response decreasing with subject weight > 95 kg (particularly for the USK 45 mg dose regimen).

During the course of the study, Centocor (the drug manufacturer) became aware that some vials of USK, not used in this trial but produced at the same location, contained black particulate matter. As a safety precaution, Centocor added a 0.22 µm filtration procedure during dose preparation. As a result of the filtration process, the volume of USK after filtration was reduced from 1.0 mL to 0.70 mL (hence, the USK dose was reduced from 90 mg to 63 mg per injection. The first 36 patients in the study (17 in Group I) were randomised prior to the filtration procedure being implemented and received USK 90 mg x 4 injections (360 mg in total). Group I subjects randomised after the filtration process was commenced (n = 59), received USK 63 mg x 4 injections (252 mg in total), and crossover patients had their Week 12 and 16 doses of USK reduced from 90 mg x 2 to 63 mg x 2 (n = 57 at Week 12 and n = 55 at Week 16). MTX use at a

dose ≤ 25 mg/week (started at least 3 months previously; stable for at least 4 weeks prior to baseline; oral or parenteral route) was allowed during the study, and 20.5% (30/146) of all subjects took concomitant MTX. No other DMARD use was permitted during the trial. During the study, just over half of all patients (54.1%; 79/146) continued taking NSAID, and no subject took low dose oral CS despite this being permissible.

There were 2 amendments to the original study protocol, both of which were implemented after the commencement of patient enrolment. The first amendment modified the exclusion criteria for prior use of anti-TNF drugs from 4 weeks to 3 months (that is, a longer washout period). The second amendment related to institution by Centocor of a filtration process during USK manufacturing.

7.1.2.1.2. Inclusion and exclusion criteria

Study C0743T10 included men and women aged 18 years or older with a diagnosis of PsA of at least 6 months duration, who had an inadequate response to standard treatment including conventional DMARDs, and/or NSAID, and/or anti-TNF drugs. Subjects with prior anti-TNF exposure for PsA or psoriasis were allowed in the trial, but overall number was limited to 20% of the total study population. Active PsA was defined as having at ≥ 3/66 swollen and ≥ 3/68 tender joints at screening and baseline; as well as having 1 of the following 2 criteria (CRP ≥ 1.5 mg/dL and/or morning stiffness ≥ 45 minutes duration). Patients were also required to have active plaque psoriasis, with a qualifying target lesion of at least 2 cm in diameter, but not located in the axilla, inframammary area, or groin.

The main exclusion criteria were

- Diagnosis – any other inflammatory arthritis or other autoimmune rheumatic disorder such as RA, AS and SLE; and pregnancy/lactation;
- Past history – substance abuse (drug or alcohol); history of chronic or recurrent infections (such as bronchiectasis, cystitis, or skin wounds), recent serious or life-threatening infection within 2 months of the baseline visit, Herpes Zoster infection within the last 2 months, or any current sign or symptom that may have indicated an infection; known TB disease, high risk of acquiring TB, or latent TB infection; history of an infected joint prosthesis at any time; concurrent infection with Hepatitis B or C virus or HIV; lymphoproliferative disorder; and malignancy within the last 5 years (except for excised basal or squamous cell skin cancers or cervical carcinoma in situ successfully treated by surgery);
- Abnormal baseline laboratory results – liver function tests > 1.5 x ULN, serum creatinine > 1.5 mg/dL, total white blood cell count < 3.5 x 109/L, neutrophil count < 1.5 x 109/L, platelet count < 100 x 109/L, or haemoglobin < 8.5 g/dL
- Recent or concurrent treatments - use of conventional DMARD therapy within 4 weeks prior to baseline (12 weeks for LEF), oral prednisone > 10 mg/day (as well as, intra-articular or parenteral CS within 4 weeks), phototherapy for skin psoriasis within 4 weeks prior to baseline, topical therapy for skin psoriasis within 2 weeks of baseline, any live virus or bacterial vaccination within 3 months of baseline; and
- Prior treatment – any exposure to biological drugs that were not anti-TNF treatment.

7.1.2.1.3. Efficacy endpoints

The primary efficacy endpoint was the rate of ACR20 response at Week 12. Major secondary endpoints (all assessed at Week 12) were ACR50 and ACR70 responses; as well as improvement from baseline in the HAQ-DI score, DLQI score and PASI score. Other efficacy assessments related to change in dactylitis and enthesitis, duration of morning stiffness, change in the DAS28 score and target lesion assessments. In addition, the rate of ACR response (20/50/70) at 36 weeks was presented according to treatment group assignment at baseline.

7.1.2.1.4. Statistical methods

All randomised subjects were included in the primary efficacy analysis. Secondary efficacy analyses were based on all randomised subjects with available outcome measurements. For categorical data, such as comparing the rate of ACR response, the CMH chi-square test was used. Continuous response parameters were compared using ANCOVA on the van der Waerden normal scores. Analyses were adjusted for prior anti-TNF exposure. All statistical tests were performed 2-sided at a significance level of 0.05.

Eligible subjects were randomised using an IVRS to receive either USK or placebo injections in a 1:1 ratio, stratified for investigational site and prior anti-TNF exposure. The sponsor was blinded through to Week 12, and the subjects and site investigators remained blinded until Week 36.

The primary analysis assumed a total enrolment of 140 subjects - 70 in each treatment group with up to 14 subjects having prior anti-TNF exposure and 56 being anti-TNF naïve. The sample size calculation assumed a 20% ACR20 response at 12 weeks in the placebo group (regardless of prior anti-TNF exposure), a 35% ACR20 response rate in the anti-TNF experienced USK treatment cohort, and a 45% ACR20 response rate in the USK treated subjects who were anti-TNF naïve. This estimation identified that the trial had 85% power to detect a significant difference in the proportion of responders between the treatment groups at a significance level of 0.05.

7.1.2.1.5. Subject disposition and protocol deviations

A total of 287 patients were screened and 146 subjects were randomised into Study C0743T10: 76 to USK and 70 to placebo. Of the 76 subjects randomised to USK at baseline, all received their first injection and 73 (96.1% of 76) received all 4 doses of USK. Of the 70 subjects in the placebo group, all received placebo injections at baseline, 57 (81.4% of 70) crossed over to receive USK at Week 12 and 55 (78.6% of 70) received USK at Week 16.

Up to Week 12, a higher proportion of subjects in the placebo group (18.6%; 13/70) permanently discontinued study medication compared to those randomised to USK (5.3%; 4/76). The 2 most common reasons for discontinuation were unsatisfactory therapeutic benefit (4 in the placebo group and 2 in the USK arm) and AEs (4 in the placebo group and 1 in the USK arm). Up to Week 36, an additional 7 subjects (5 in the placebo crossover group and 2 in the USK arm) discontinued study treatment. Four of the additional cases discontinued because of lack of efficacy (2 in each treatment group) and 3 ceased due to AEs (2 in the placebo crossover cohort and 1 in the USK arm).

Protocol deviations were categorised into 3 domains and affected a similar proportion of subjects in each treatment group. The domains and corresponding incidence were:

- Not meeting study entry criteria – 7.1% (5/70) in the placebo group and 5.3% (4/76) in the USK arm,
- Variations study drug administration – 31.4% (22/70) in the placebo group and 30.3% (23/76) in the USK arm. All but 1 case (in the USK group) was due to study drug being given outside of the protocol defined study visit window (+/- 3 days), and
- Use of prohibited concomitant medications – 11.4% (8/70) in the placebo group and 13.2% (10/76) in the USK arm. In 8 of the 18 cases (3 in the placebo group and 5 in the USK arm), the prohibited concomitant medication was the initiation of anti-TNF medication, usually late in trial (Week 28).

7.1.2.1.6. Baseline data

The treatment groups were similar with respect to demographic characteristics and baseline PsA features. Overall, subjects had a median age of 49 years (range: 23 - 74 years), median weight 90.9 kg, just over half (56.2%; 82/146) were male, and the majority (94.5%; 138/146)

were of Caucasian ethnicity. The median duration of PsA for all subjects was 5.22 years, and the median duration of psoriasis 16.92 years. Subjects in the placebo group had a median duration of psoriasis more than 3 years than the USK arm (15.12 years versus 18.89 years, respectively).

In terms of PsA disease activity at baseline, the median numbers of tender and swollen joints were lower for the placebo group (16.0 and 7.0, respectively) compared to the USK arm (19.5 and 10.0, respectively). The mean HAQ-DI scores were similar in both treatment groups at 0.8 - 0.9. The mean CRP was 0.9 mg/dL (median 0.4 mg/dL) in the USK group and 0.8 mg/dL in the control arm (median 0.7 mg/dL).

Less than half of all patients (45.2%; 66/146) had enthesitis at baseline, and 22.6% (33/146) had current dactylitis. In the patients with ≥ 3% BSA psoriasis skin involvement at baseline (n = 60 in the placebo group and n = 64 in the USK arm), the median PASI score was 8.7 and the median DLQI score was 10.5. Both of these skin related scores were similar between the 2 treatment groups.

Most subjects (92.5%) had prior exposure to topical therapies for psoriasis, 52.7% of patients had previously taken MTX and 61.0% of subjects had used at least 1 DMARD (including MTX) prior to entering the trial. In total, 40 subjects (27.4% of 146) had prior experience with 1 or more biologic drugs for either PsA or psoriasis. A higher proportion of patients in the control group (31.4%; 22/70) had prior exposure to biologic drugs than the USK arm (23.7%; 18/76). The 3 most commonly used prior anti-TNF drugs were etanercept (14.4%; 21/146), alefacept (8.2%; 12/146) and infliximab (6.2%; 9/146). Approximately half of the biologic experienced patients (19/40) had taken such drugs for > 12 months.

The incidence of relevant co-morbid conditions was similar in the treatment groups. Regarding risk factors for cardiovascular disease, a past history of hypertension was recorded in 34.2% of all subjects, 26.0% reported hyperlipidaemia, 12.3% recorded diabetes mellitus (including 2.7% requiring insulin), and 29.5% were current smokers.

7.1.2.1.7. Results for efficacy endpoints

The percentage of patients achieving ACR20 response at Week 12 (primary efficacy endpoint) was significantly greater in the USK group (42.1% [32/76]; p < 0.001) compared with the placebo arm (14.3%; 10/70). A per protocol analysis including subjects who received all 4 correct injections within 2 weeks of the scheduled visit dates supported the primary analysis with a higher ACR20 response in the USK group versus placebo (45.7% [32/70] versus 16.9% [10/59]; p < 0.001).

At Week 12, a statistically greater proportion of subjects treated with USK achieved an ACR50 (25.0% [19/76] versus 7.1% [5/70]; p = 0.004) and ACR70 response compared with the control group (10.5% [8/76] versus 0; p = 0.005). The median (and mean) change from baseline to Week 12 in the HAQ-DI score was statistically greater in the USK group (n = 75; median - 0.25; mean - 0.31 +/- 0.394; p < 0.001) compared with the placebo arm (n = 64; median 0; mean - 0.04 +/- 0.447).

In the subgroup of patients with ≥ 3% BSA psoriasis skin involvement at baseline, a significantly greater percentage of patients in the USK group achieved PASI 75 response at 12 weeks (52.4% [33/63]; p < 0.001) versus those in the control arm (5.5%; 3/55). The rate of PASI 75 response peaked at Week 12 and declined thereafter to 36 weeks of follow-up. In the same subgroup of subjects with ≥ 3% BSA psoriasis at baseline, those treated with USK had a statistically greater decrease (improvement) in their median and mean DLQI scores (n = 63; median - 6.0; mean - 8.6 +/- 7.69; p < 0.001) compared with subjects in the placebo group (n = 55; median 0; mean - 0.8 +/- 5.42). At Week 12, subjects in the USK group demonstrated significantly greater median percentage improvements from baseline in the target lesion score compared to those in the placebo arm (USK: n = 75; 60.0% median percentage improvement versus placebo: n = 65; no median percentage change).

Between baseline and Week 12, the overall proportion of subjects suffering dactylitis did not change in either the USK or placebo group, but there was a statistically greater median decrease in the dactylitis score at 12 weeks for those who received USK (- 2.0; p = 0.011) versus those in the control group (no change). At Week 12, the proportion of patients with enthesopathy was significantly lower in the USK treatment arm (23.0% [17/74]; p = 0.016) compared to those in the control group (42.2%; 27/64).

At Week 12, a significantly greater proportion of patients in the USK treatment group were DAS28 responders (57.5% [42/73]; p = 0.001) compared to the placebo arm (30.2%; 19/63). The percentage improvement from baseline to Week 12 in the duration of morning stiffness (in minutes) was significantly greater in the USK treated subjects (median decrease of 50% from a baseline median of 90 minutes; p = 0.003) compared to those in the placebo group (zero median decrease from a baseline median of 90 minutes).

Table 16 summarises the rate of ACR response between Weeks 12 and 36. The rate of ACR20 response in the original USK treatment group at 36 weeks (34.3%; 23/67) was approximately 80% of what was observed at Week 12 (42.1%; 32/76) with a diminishing rate of ACR response observed after Week 28 (that is, losing response to USK – last dose administered at Week 4). In the assessment visits that occurred between weeks 12 and 36, the rate of ACR response in the original USK treatment group peaked at Week 16. For the patients in the original placebo group who crossed over to USK at Weeks 12 and 16, the rate of ACR20/50/70 response at 36 weeks was 42.0% (21/50), 14.0% (7/50) and 6.0% (3/50), respectively. Their rate of ACR response appeared to peak at Week 24 (that is, 12 weeks after the initiation of USK).

Table 16: Number and Percentage of Randomised Subjects with ACR20, ACR50 and ACR70 Response between Weeks 12 and 36 in Study C0743T10.

	Placebo → CNTO 1275 × 2 (at Week 12)	CNTO 1275 × 4
Week 12		
n	70	76
ACR 20	10 (14.3%)	32 (42.1%)
ACR 50	5 (7.1%)	19 (25.0%)
ACR 70	0 (0.0%)	8 (10.5%)
Week 16		
n	56	75
ACR 20	25 (44.6%)	37 (49.3%)
ACR 50	11 (19.6%)	25 (33.3%)
ACR 70	4 (7.1%)	13 (17.3%)
Week 20		
n	53	73
ACR 20	24 (45.3%)	32 (43.8%)
ACR 50	12 (22.6%)	20 (27.4%)
ACR 70	5 (9.4%)	12 (16.4%)
Week 24		
n	55	70
ACR 20	28 (50.9%)	29 (41.4%)
ACR 50	15 (27.3%)	21 (30.0%)
ACR 70	5 (9.1%)	12 (17.1%)
Week 28		
n	53	71
ACR 20	24 (45.3%)	30 (42.3%)
ACR 50	15 (28.3%)	20 (28.2%)
ACR 70	5 (9.4%)	11 (15.5%)
Week 36		
n	50	67
ACR 20	21 (42.0%)	23 (34.3%)
ACR 50	7 (14.0%)	11 (16.4%)
ACR 70	3 (6.0%)	7 (10.4%)

7.2. Analyses performed across trials (pooled analyses and meta-analyses)

To evaluate the potential effect of USK on the X-ray progression of PsA in adult patients with active disease, it was pre-specified that the 2 pivotal Phase III Studies (PSUMMIT I and II) would have their data combined in an integrated analysis to assess this outcome.

7.2.1. Rationale for integrated analysis of radiographic data

In addition to examining the effects of USK on the symptoms and signs of PsA, the USK clinical development program intended to evaluate the effects of USK on the progression of structural damage in patients with active PsA. However, initial power calculations determined that at least 900 subjects would be required to demonstrate a clinically relevant benefit. To accomplish the goals of the program, 2 Phase III studies of similar design with contemporaneous subject enrolment, requiring the same PsA disease eligibility criteria, and using the same USK dosing regimens were undertaken. The key difference between the 2 studies was that PSUMMIT I recruited anti-TNF naïve subjects (n = 615), while the PSUMMIT II trial enrolled a mixture of anti-TNF experienced (n = 180) and anti-TNF naïve (n = 132) patients.

7.2.2. Radiographic assessments

Plain X-rays of the hands and feet were taken in a standardised manner at baseline, Week 24 and Week 52 in both Phase III studies (regardless of early escape status), or at the time of discontinuation of study medication (unless performed within the previous 8 weeks). Radiographs were digitised and read at a central location by the same 2 expert independent readers in both Phase III studies (between June 2011 and November 2012), and the average of both scores derived the final result for each subject. A third reader was available to adjudicate on X-rays when the 2 primary readers recorded a total modified vdH-S score with an absolute difference > 10 points, or if the score of 1 reader was missing. If the > 10 point score difference occurred, then the adjudicator result replaced 1 of the primary reader scores, and an average of the 2 results was recorded. X-rays were evaluated in a random order without knowledge of chronology, subject identity or treatment assignment. Good intra-reader and inter-reader agreements were demonstrated.

The van der Heijde-Sharp scoring method (vdH-S) modified for PsA was used to assess structural joint damage, and its progression (van der Heijde et al, 2005). The PsA modified vdH-S score is the sum of the joint space narrowing (JSN) score plus the erosion score (ES) and has a range of 0 - 528. A higher score indicates more radiographic damage, and a positive change in the score represents radiographic progression. The total score consists of the composite of the JSN (range of 0 - 208; 26 sites [20 joints in the hands and 6 in the feet] on each side of the body scored from 0 - 4 for each site) and the ES (range of 0-320; 26 sites [20 joints in the hands and 6 in the feet] on each side of the body). Erosions in each hand are scored from 0 (no erosion) to 7 (gross osteolysis). However, for scores of 6 (pencil-in-cup abnormality) and 7, a maximum score of 5 is assigned for the total calculation.

7.2.3. Radiographic endpoints

The major radiographic endpoint (also nominated as a key secondary efficacy endpoint in the clinical development program) was the mean change from baseline to Week 24 in the total modified vdH-S score of the hands and feet, and was based on the integrated analysis of the combined data from the 2 pivotal Phase III studies. To control for multiplicity, the primary X-ray analysis compared the combined USK group (45 and 90 mg dose arms) with the placebo group first, and if this result was significant then each of the USK dose groups were compared to placebo.

Additional X-ray analyses (at Weeks 24 and 52) based on the combined Phase III trial data included:

- Change from Week 24 to 52 in total modified vdH-S score

- Change from baseline in total modified vdH-S score assessed by type of damage (erosions and JSN) and anatomic region (hands or feet)
- Proportion of subjects with no radiographic progression (defined in 3 different ways as the change from baseline in modified vdH-S by ≤ 0, ≤ 0.5 and the Smallest Detectable Change (SDC), and
- Proportion of patients with pencil-in-cup and gross osteolysis deformities.

The SDC is defined as the amount of change from baseline for which any smaller change cannot be reliably distinguished from random error in the measurement. At 24 weeks, the SDC for the change in the total modified vdH-S score was 2.01.

Furthermore, the following analyses were performed for each individual trial:

- Change from baseline in total modified vdH-S score at Weeks 24 and 52
- Change from baseline in total modified vdH-S score assessed by type of damage (erosions and JSN) and anatomic region (hands or feet) at Week 24 only, and
- Proportion of subjects with no radiographic progression (defined as the change from baseline in modified vdH-S by ≤ 0, and ≤ 0.5) at Weeks 24 and 52.

7.2.4. Statistical methods and data handling rules

Descriptive statistics were used for the radiographic analyses. Continuous data such as the change from baseline in the total modified vdH-S score were compared using ANCOVA on the van der Waerden normal scores, adjusted for baseline MTX usage (yes/no) and study effect (PSUMMIT I or PSUMMIT II). Analyses suitable for categorical data such as the proportion of subjects achieving no X-ray progression were compared using chi-square or CMH test, adjusted for baseline MTX usage (yes/no). All statistical tests were 2-sided at a significance level of $\alpha = 0.05$.

The integrated X-ray analysis included all randomised patients, irrespective of early escape. In the circumstance of a missing X-ray score, 2 methods were used for imputation. Firstly, linear extrapolation of the scores from the last 2 radiographs taken on study before Week 52 (using X-rays taken at least 8 weeks apart) was used for the handling of missing data. Alternatively, if X-ray data was insufficient for linear extrapolation, the median of the change in the total scores based on all patients within the same MTX stratum at the same visit was assigned (subsequently zero for all dosing regimens). Sensitivity analyses were performed for the major radiographic endpoint of the change from baseline in total vdH-S score using the removal of those who did complete their original assigned therapy, as well as only evaluating the observed data set. To assess the consistency of efficacy, various subgroup analyses were performed including data such as demographic characteristics, baseline PsA features, and baseline and prior treatment.

7.2.5. Baseline data

Overall, 1771 patients were screened for the 2 Phase III studies, of whom 927 subjects (747 anti-TNF naïve and 180 anti-TNF experienced) were randomised to treatment: 310 patients in the placebo group (62 anti-TNF experienced), 308 in the USK 45 mg arm (60 anti-TNF exposed) and 309 in the USK 90 mg group (58 anti-TNF experienced). Demographics and baseline disease severity data have been provided earlier in this report. In general, the baseline clinical disease characteristics including swollen and tender joint counts, and CRP were comparable between study populations in the PSUMMIT I and II studies, and were generally comparable across each treatment group within each study, with the exception of CRP levels. In the PSUMMIT I Study, subjects in the USK 90 mg group had higher median baseline serum CRP levels (12.3 mg/L) than patients in either the USK 45 mg (10.0 mg/L) or placebo group (9.6 mg/L). In the PSUMMIT II trial, subjects in the placebo group had lower median baseline serum CRP levels (8.5 mg/L) than subjects in either the USK 45 mg (13.0 mg/L) or USK 90 mg groups (10.1 mg/L). Additionally, in

the PSUMMIT II Study, subjects with prior exposure to anti-TNF treatment had a higher number of swollen and tender joints, and increased CRP levels compared to subjects who were naïve to anti-TNF drugs. Approximately 50% of subjects in each study were on concomitant MTX and at least 80% of patients had used at least 1 DMARD previously. In the PSUMMIT II Study, 58% of subjects had prior exposure to anti-TNF therapy, of which over 70% had discontinued this treatment for a lack of efficacy or intolerance.

Baseline vdH-S scores by type (erosion and JSN), anatomic region (hands and feet) and the total score for the combined dataset were comparable across the 3 randomised treatment groups – refer to Table 17. The mean (SD) vdH-S score was slightly higher in the USK 45 mg group (30.4 +/- 50.7) compared to the USK 90 mg arm (28.0 +/- 42.2) and control group (28.0 +/- 55.8). In each of the treatment groups, the erosion and JSN scores were equal contributors to the overall score, and changes in the hands accounted for approximately 60% of the overall score versus the feet (approximately 40%). In the PSUMMIT I Study, the mean baseline total radiographic scores (29.0 +/- 51.5) were comparable across the 3 treatment groups. In the PSUMMIT II trial, the mean baseline total radiographic scores were slightly lower in the placebo (24.3 +/- 48.0) and USK 90 mg groups (26.9 +/- 42.6) compared with the USK 45 mg arm (31.1 +/- 48.9). In addition, subjects with prior exposure to anti-TNF treatment had lower radiographic scores at baseline (27.6 +/- 44.2) compared with those naïve to anti-TNF (30.1 +/- 47.1).

Table 17: Summary of Total Modified vdH-S Scores at Baseline in the Combined Dataset.

		Ustekinumab			
	Placebo	45 mg	90 mg	Combined	Total
Subjects randomized	310	308	309	617	927
Total score					
N	306	303	300	603	909
Mean (SD)	28.01 (55.771)	30.40 (50.688)	27.97 (42.137)	29.19 (46.607)	28.79 (49.853)
Median	9.50	11.50	10.50	11.00	11.00
IQ range	(3.00; 29.50)	(3.50; 33.50)	(3.50; 34.50)	(3.50; 34.00)	(3.00; 32.64)
Range	(0.0; 500.5)	(0.0; 310.3)	(0.0; 346.0)	(0.0; 346.0)	(0.0; 500.5)

7.2.6. Patient disposition and handling of missing data

Using the combined dataset at Week 24, a total of 71 (7.7% of 927) subjects in the study had discontinued with a much higher rate of withdrawal in the placebo group (12.6%; 39/310) than the USK 45 mg (4.5%; 14/308) and USK 90 mg (5.8%; 18/309) arms. The most common reason for discontinuation of study medication across all 3 treatment groups by Week 24 was AEs (3.1%; 29/927) followed by lack of efficacy (2.3%; 21/927).

For the integrated dataset, the overall rates of missing radiographic data were low in all 3 groups (2.3 - 10.3%) and would not be expected to significantly impact the overall interpretation of the X-ray results. Most subjects (91.0%; 844/927) had both baseline and Week 24 radiographs for assessment. Of the 83 subjects with missing X-ray data, 24 (2.6% of 927) required linear extrapolation of radiographic results at Week 24, and 59 (6.4% of 927) required imputation with median change (subsequently attributed as zero) because they lacked either baseline or post-baseline X-rays (predominately, post-baseline X-rays were missing) – refer to Table 18. The PSUMMIT I and II trials differed in terms of the amount and pattern of missing X-ray data. The highest rate of missing data (18.8%; 34/180) was observed in the anti-TNF exposed cohort in the PSUMMIT II Study. This principally occurred because of the high rate of early discontinuations (often within 8 weeks of commencement), and was more than 2-fold higher in the placebo group versus the USK treatment arms, particularly those with prior anti-TNF exposure.

Table 18: Number of Subjects Requiring Missing Data Imputation in the Combined X-Ray Dataset.

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Ustekinumab Combined	Total
Randomized subjects in 3001 and 3002	310	308	309	617	927
Requiring median imputation	32 (10.3%)	12 (3.9%)	15 (4.9%)	27 (4.4%)	59 (6.4%)
Requiring linear extrapolation	7 (2.3%)	7 (2.3%)	10 (3.2%)	17 (2.8%)	24 (2.6%)
Randomized subjects in 3001	206	205	204	409	615
Requiring median imputation	12 (5.8%)	6 (2.9%)	5 (2.5%)	11 (2.7%)	23 (3.7%)
Requiring linear extrapolation	3 (1.5%)	5 (2.4%)	5 (2.5%)	10 (2.4%)	13 (2.1%)
Randomized subjects in 3002	104	103	105	208	312
Requiring median imputation	20 (19.2%)	6 (5.8%)	10 (9.5%)	16 (7.7%)	36 (11.5%)
Requiring linear extrapolation	4 (3.8%)	2 (1.9%)	5 (4.8%)	7 (3.4%)	11 (3.5%)
Previously treated with anti-TNFa	62	60	58	118	180
Requiring median imputation	15 (24.2%)	4 (6.7%)	7 (12.1%)	11 (9.3%)	26 (14.4%)
Requiring linear extrapolation	3 (4.8%)	2 (3.3%)	3 (5.2%)	5 (4.2%)	8 (4.4%)
Anti-TNFa naive	42	43	47	90	132
Requiring median imputation	5 (11.9%)	2 (4.7%)	3 (6.4%)	5 (5.6%)	10 (7.6%)
Requiring linear extrapolation	1 (2.4%)	0	2 (4.3%)	2 (2.2%)	3 (2.3%)

7.2.7. Result for major radiographic endpoint

The major radiographic endpoint was the change from baseline to Week 24 in the total modified vdH-S score of the hands and feet for the combined X-Ray data from the PSUMMIT I and II studies.

Across all 3 treatment groups the median change from baseline in total modified vdH-S score was 0 at Week 24 – refer to Table 19. However, the mean change from baseline in the total modified vdH-S score at Week 24 was significantly less (that is, indicating less X-ray progression) for subjects in the combined (0.40 +/- 2.26), 45 mg (0.40 +/- 2.11) and 90 mg USK groups (0.39 +/- 2.40) compared with subjects in the placebo arm (0.97 +/- 3.85). Sensitivity analyses for this endpoint supported a similar pattern of less radiographic progression for USK treated subjects versus control patients at Week 24. Both doses of USK appeared to be equally efficacious in achieving this outcome.

Table 19: Summary of Change from Baseline to Week 24 in the total modified vdH-S Score.

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Ustekinumab Combined
Subjects randomized	310	308	309	617
Change from baseline				
N	310	308	309	617
Mean (SD)	0.97 (3.852)	0.40 (2.110)	0.39 (2.403)	0.40 (2.260)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 1.00)	(0.00; 0.50)	(0.00; 0.50)	(0.00; 0.50)
Range	(-3.0; 58.0)	(-9.5; 14.0)	(-6.0; 27.0)	(-9.5; 27.0)
p-value[a]		0.017	<0.001	<0.001
p-value[b]		0.018	< 0.001	< 0.001

[a] Based on re-randomization test.
[b] Based on van der Waerden test.

Subgroup analyses were also performed for the change from baseline to Week 24 in the total modified vdH-S score by demographics including baseline subject weight (≤ 100 kg versus > 100 kg), baseline disease characteristics and prior and concomitant treatment. In subjects weighing ≤ 100 kg, which constituted approximately 75% of the enrolled subject population, less progression of structural damage was observed in USK-treated versus placebo-treated subjects. In subjects weighing > 100 kg, no treatment effect was seen in subjects receiving USK treatment when compared to placebo treated subjects, though the number of subjects in this

subpopulation was smaller, and the magnitude of progression of structural damage was low in the placebo group – refer to Table 20. The observation of less progression of structural damage in obese subjects has been previously reported in RA subjects though the mechanistic basis of this observation has not been determined (Baker et al, 2011).

Table 20: Summary of Change from Baseline to Week 24 in vdH-S Score by Subject Weight.

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	310	308	309	617
Change from baseline				
Subjects with weight ≤ 100 kg at baseline				
N	228	227	227	454
Mean (SD)	1.21 (4.406)	0.34 (2.191)	0.26 (1.556)	0.30 (1.899)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 1.50)	(0.00; 0.50)	(0.00; 0.50)	(0.00; 0.50)
Range	(-3.0; 58.0)	(-9.5; 14.0)	(-4.5; 8.2)	(-9.5; 14.0)
Subjects with weight >100 kg at baseline				
N	82	81	81	162
Mean (SD)	0.31 (1.263)	0.58 (1.865)	0.76 (3.898)	0.67 (3.048)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 0.50)	(0.00; 1.00)	(0.00; 0.50)	(0.00; 0.50)
Range	(-3.0; 5.5)	(-5.0; 10.0)	(-6.0; 27.0)	(-6.0; 27.0)

No significant differences in treatment response relating to disease characteristics (for example, pattern of PsA) were identified by the subgroup analysis of the major radiographic endpoint. Inhibition of radiographic progression was observed for subjects receiving either dose of USK compared with placebo, regardless of prior or concomitant use of MTX, or any other prior conventional DMARD. However, subjects with prior exposure to anti-TNF drugs (PSUMMIT II Study cohort), who received USK (45 mg or 90 mg) did not demonstrate a treatment effect for the change from baseline in their total modified vdH-S scores at Week 24, compared with subjects treated with placebo – refer to Table 21. This was also true for subjects without prior anti-TNF exposure in this study – refer to Table 22. It is unclear why the results of the PSUMMIT II Study have not demonstrated a treatment effect with USK but the sponsor proposes that the results of this trial may have been confounded by the large amount and non-random pattern of missing radiographic data, particularly in the placebo group.

Table 21: Summary of Change from Baseline to Week 24 in vdH-S Score in PSUMMIT II (Anti-TNF exposed subjects).

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	62	60	58	118
Change from baseline				
N	62	60	58	118
Mean (SD)	0.59 (2.114)	0.66 (2.834)	1.13 (4.481)	0.89 (3.727)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 0.00)	(0.00; 0.50)	(0.00; 0.50)	(0.00; 0.50)
Range	(-2.5; 10.5)	(-8.1; 14.0)	(-2.5; 27.0)	(-8.1; 27.0)
p-value		0.865	0.752	0.956

Table 22: Summary of Change from Baseline to Week 24 in vdH-S Score in PSUMMIT II (Anti-TNF naive subjects).

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	42	43	47	90
Change from baseline				
N	42	43	47	90
Mean (SD)	0.40 (1.470)	0.66 (1.636)	0.41 (1.910)	0.53 (1.779)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 0.50)	(0.00; 1.00)
Range	(-3.0; 4.5)	(-2.0; 7.5)	(-2.5; 8.2)	(-2.5; 8.2)
p-value		0.345	0.852	0.669

7.2.8. Results for other x-ray endpoints

7.2.8.1. Change from week 24 to week 52 in total modified vdH-S score

Mean changes in total modified vdH-S scores observed between Week 24 and 52 for the USK treatment groups (0.18 for 45 mg and 0.26 for 90 mg) were less than those that occurred between baseline and Week 24 (0.40 for 45 mg and 0.39 for 90 mg), indicating that the impact of USK on the inhibition of the progression of structural damage was maintained through to Week 52. Subjects randomised to placebo who began USK 45 mg at Week 16 or 24 demonstrated a substantial reduction in the rate of radiographic progression between weeks 24 and 52 (0.08) compared with the rate of radiographic progression for the placebo group from baseline to Week 24 (0.97).

7.2.8.2. Change from baseline by type of damage and anatomic location

At 24 weeks, USK treated subjects demonstrated significantly less change from baseline in ES (mean change of 0.23 [p = 0.002] for the 45 mg group, 0.19 [p < 0.001] for the 90 mg arm and 0.21 [p < 0.001] for the combined USK cohort) compared with 0.57 for the placebo group. Numerically less progression in JSN was also observed for each USK group as compared with placebo (mean change: 0.17 [p = 0.466] and 0.20 [p = 0.112] for the 45 mg and 90 mg groups, respectively, compared with 0.40 for placebo). Regarding mean change from baseline to Week 24 by anatomic region (hands or feet), the USK 90 mg group recorded significantly less progression (p < 0.05 for each comparison) than the placebo arm for the total score and ES in the foot and hand, but only the JSN score in the hands (that is, the differences in JSN score change in the feet did not reach statistical significance). Compared with placebo, the change from baseline in the modified vdH-S score for the USK 45 mg group for all of the hand scores (total, ES and JSN) reached statistical significance but only the ES in the feet achieved statistical significance over placebo. At Week 52, the change from baseline in modified vdH-S scores by type of damage (erosions or JSN) or region (hands or feet) was consistent with that seen for the total modified vdH-S scores at Week 24.

7.2.8.3. Proportion of subjects with no radiographic progression

The proportions of subjects who had no progression of structural damage, analysed as subjects who had either a change from baseline in the total modified vdH-S score of ≤ 0 or ≤ 0.5 or the SDC supported the efficacy of USK. A numerically greater proportion of subjects in both the USK 45 mg (65.3%; 201/308) and 90 mg groups (70.6%; 218/309) achieved ≤ 0 change in the total modified vdH-S score compared with the placebo group (64.5%; 200/310), but this analysis did not reach statistical significance. However, when observed data were used, reflecting the removal of imputed data, statistical significance was reached for the USK 90 mg group (69.0%; 196/284) versus control (59.8% [162/271]; p = 0.026).

A significantly greater proportion of subjects in the USK 90 mg (80.3% [248/309]; p = 0.024) group achieved ≤ 0.5 change in total modified vdH-S score over the initial 24 weeks compared with the placebo group (72.6%; 225/310). The USK 45 mg group (76.9%; 237/308) did not achieve a statistically significant result in comparison to placebo. Similarly, when observed data

were used, the statistical significance level for the placebo comparison (69.0%; 187/271) was reached for the USK 90 mg group (79.2% [225/284]; p = 0.007), but not with the USK 45 mg group (76.1% [220/289]; p = 0.062).

When the 24 week data was analysed by the proportion of subjects with progression of structural damage based on the SDC criteria and using the observed data, a statistically significant lower proportion of subjects in both USK dose groups demonstrated progression of structural damage based on the total modified vdH-S score (8.3% [24/289] for the 45 mg group and 8.1% [23/284] for the 90 mg arm) as compared with the placebo group (16.2%; 44/271). This result (for both USK dose groups) was achieved by a statistically lower rate of erosive progression as the JSN scores were numerically, but not significantly lower by independent analysis.

The proportion of subjects with X-ray progression at Week 52 (by any cut-off standard) were increased slightly compared with the results observed at Week 24, and was higher in the placebo crossover group than the USK treatment arms. The proportions of subjects with radiographic progression between weeks 24 and 52 were comparable between the 3 treatment groups.

7.2.8.4. Proportion of subjects with pencil-in-cup and gross osteolysis

The proportion of patients with pencil-in-cup or gross osteolysis deformities at baseline were low at baseline (2.6 - 3.8% of subjects in each treatment group) and remained stable at both 24 and 52 weeks (3.0 - 3.8%).

7.2.8.5. Individual study comparison

The effect of USK on inhibition of the progression of structural damage was also evaluated independently for subjects from the PSUMMIT I and II studies. Consistent with the integrated analysis, subjects participating in the PSUMMIT I trial who received either USK 45 mg or 90 mg demonstrated significantly less progression from baseline in their total modified vdH-S scores at Week 24 compared with placebo-treated subjects (regardless of whether imputed or observed data was used) – refer to Table 23.

Table 23: Summary of Change from Baseline to Week 24 in vdH-S Score in PSUMMIT I.

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	206	205	204	409
Change from baseline				
N	206	205	204	409
Mean (SD)	1.20 (4.520)	0.28 (1.943)	0.17 (1.446)	0.23 (1.712)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 1.50)	(0.00; 0.50)	(-0.25; 0.50)	(0.00; 0.50)
Range	(-3.0; 58.0)	(-9.5; 13.0)	(-6.0; 6.5)	(-9.5; 13.0)
p-value		0.001	< 0.001	< 0.001

However, no treatment effect with USK over placebo was noted in the PSUMMIT II Study as the mean change from baseline in total modified vdH-S scores at Week 24 was similar across all treatment groups (using either imputed or observed data) – refer to Table 24. While differences in treatment effect between the 2 pivotal Phase III studies may derive from the smaller size and heterogeneity of the PSUMMIT II population, the trials also differed in the volume of the missing X-ray data. The PSUMMIT II Study had a higher incidence of missing data (particularly, in the anti-TNF experienced, placebo treated patients) for which the data handling rules may have impacted upon significantly. As most of the missing X-ray data required median imputation, the pre-specified median imputation rules (attributed score = 0) may have conservatively favoured the placebo group. Nonetheless, the effect of USK on progression of structural damage in PsA patients who have received previous anti-TNF treatment has not been established.

Table 24: Summary of Change from Baseline to Week 24 in vdH-S Score in PSUMMIT II.

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects randomized	104	103	105	208
Change from baseline				
N	104	103	105	208
Mean (SD)	0.51 (1.875)	0.66 (2.398)	0.81 (3.571)	0.73 (3.040)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 0.50)	(0.00; 1.00)	(0.00; 0.50)	(0.00; 0.50)
Range	(-3.0; 10.5)	(-8.1; 14.0)	(-2.5; 27.0)	(-8.1; 27.0)
p-value		0.605	0.965	0.755

For the individual study analysis, the change from baseline in the total modified vdH-S score assessed by type of damage (erosions and JSN) and anatomic region (hands or feet) at Week 24, and the proportion of subjects with no radiographic progression (defined by the 3 criteria outlined previously) showed the same pattern of response identified for the total modified vdH-S score. No treatment effect with USK over placebo was noted in the PSUMMIT II Study, but the PSUMMIT I trial showed a consistent treatment effect in favour of USK versus control for all of the supporting X-ray endpoints (that is, the individual components comprising the total score, as well as various criteria defining no radiographic progression).

7.3. Evaluator's conclusions on clinical efficacy for Indication 1

'Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms, including the inhibition of structural damage, of active psoriatic arthritis in adult patients (18 years or older).'

This submission contains 2 pivotal Phase III studies (PSUMMIT I and II) in adult subjects with PsA, and 1 non-pivotal, Phase II trial (Studies C0743T10) to support the extension of treatment indication. One of the pivotal studies (PSUMMIT I) is ongoing with a planned 108 weeks of treatment follow-up. In this submission, both Phase III studies submitted a 52 week efficacy report. Both Phase III studies recruited adult patients with active disease (well defined) and the diagnosis of PsA was in accordance with best practice (that is, using the CASPAR diagnostic criteria). Both of the Phase III had a 16 week placebo controlled period and the primary efficacy endpoint was assessed at 24 weeks. The supporting Phase II study (C0743T10) assessed the primary efficacy outcome at 12 weeks but continued collecting data up to 36 weeks.

This submission is seeking an indication in active PsA, and in general is consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EMEA guideline CPMP/EWP/438/04 '*Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis*' (effective 5 February 2008). In the Phase III trials, the choice of clinical (joints and skin), physical functioning and QOL endpoints, as well as the statistical analysis were appropriately performed.

The baseline demographic and disease related characteristics of patients in each of the 3 studies are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. However, there are some caveats to the generalisability of the treatment population. For example, all of the trials excluded patients who were at a significant risk of infection, or who had various abnormal laboratory results at baseline (for example, abnormal haematology or liver function tests).

The pivotal trials enrolled patients with moderately-severely active PsA, and demonstrated that USK is an effective treatment in those who have either failed to respond to conventional treatment options, such as DMARDs (mainly MTX) and/or NSAID. In a significant subset of patients in the PSUMMIT II (as well as Study C0743T10) trial, exposure to 1 or more anti-TNF drugs was additionally documented. The primary efficacy endpoint of both Phase III studies was the proportion of subjects who achieved an ACR20 response at 24 weeks (that is, clinical

response criteria), and this was achieved in both trials. In the PSUMMIT I Study, more patients treated with USK (42.4% [87/205] treated with 45 mg injections and 49.5% [101/204] receiving 90 mg) achieved this outcome versus 22.8% (47/206) of patients in the placebo group. In the PSUMMIT II Study, the ACR20 response rates showing a similar benefit in favour of USK, but at not such an overall level of response. This probably reflects the treatment refractory nature of this population compared to the PSUMMIT I study cohort. In the PSUMMIT II Study, more patients treated with USK (43.7% [45/103] treated with 45 mg and 43.8% [46/105] receiving 90 mg) achieved an ACR20 response at 24 weeks versus 20.2% (21/104) of patients in the placebo group. Many secondary efficacy measures examining other clinical outcomes (enthesitis and dactylitis scores) and functional endpoints (HAQ-DI) also demonstrated clinically significant changes with USK. Additionally, improvements in measures of skin disease activity (PASI response) and health related QOL were also attained with USK therapy. USK also showed efficacy in the subgroup of patients with co-existent inflammatory spondylitis but the BASDAI score has not been validated in subjects with PsA. In the 2 pivotal Phase III studies, clinical response was maintained for up to 52 weeks of treatment but observations taken after 24 weeks were not placebo controlled. The supporting Study C0743T10 supported the observation that USK therapy results in clinically meaningful improvements in joint disease activity. Clinical response to USK appears to peak approximately 12 weeks after treatment initiation.

Although the 2 pivotal Phase III studies were not designed to compare the efficacy of concomitant MTX, or of anti-TNF experienced versus anti-TNF naïve groups, USK demonstrated superior efficacy compared to control therapy regardless of concurrent MTX use and, importantly among the majority of anti-TNF experienced patients, although to a lesser degree than that observed in anti-TNF naïve subjects. For the subset of patients (n = 45) in the PSUMMIT II trial who had used 3 or more anti-TNF drugs previously, the rate of ACR20 response at 24 weeks between USK and placebo showed no significant treatment related difference. Consistently, patients in both the PSUMMIT I and II studies weighing > 100 kg demonstrated lower overall rates of clinical response (joints and skin) than those weighing ≤ 100 kg. Pharmacokinetic factors (lower mean serum USK concentrations) may contribute to the observation of lower overall clinical response in patients weighing > 100 kg. In the PSUMMIT I Study (but not the PSUMMIT II trial), the USK 90 mg dose showed a numerical advantage over the USK 45 mg dose in achieving various levels of ACR response in the subgroup of patients weighing > 100 kg. Such an observation supports the proposed dosing regimen of using 90 mg USK injections (versus USK 45 mg therapy) in subjects weighing > 100 kg.

To determine the effect of USK on the inhibition of structural progression an integrated analysis of the X-ray data from both Phase III studies was pre-specified. This was a major secondary efficacy endpoint of the clinical study program. The primary X-ray endpoint was the mean change from baseline to Week 24 in the total modified vdH-S score. This was achieved using the combined dataset. However, when the individual trials were analysed independently the beneficial radiographic effect of USK was only observed in the PSUMMIT I cohort and no treatment related effect was observed in the PSUMMIT II Study. The sponsor proposes that the results of this trial may have been confounded by the large amount and non-random pattern of missing radiographic data, particularly in the placebo group. In addition, for subjects weighing > 100 kg, no treatment effect was seen in subjects receiving USK treatment when compared to placebo treated subjects, though the number of subjects in this subpopulation was smaller, and the magnitude of progression of structural damage was low in the placebo group.

Overall, the data in this submission supports the efficacy of USK in the treatment of active PsA from a clinical perspective (that is, in beneficially treating the symptoms and signs, as well as improving physical functioning) in those with moderate-severely active disease at baseline, with or without concurrent DMARD and/or NSAID. Approximately half of all subjects in the 3 PsA studies took MTX concurrently with USK, and the beneficial clinical responses in those not

taking concomitant MTX were similar. Hence the sponsor has justified the claim of using USK in patients with PsA with or without MTX.

However, the current submission does not provide a sufficiently robust dataset for the claimed additional feature of inhibition of structural progression (as measured by X-ray of peripheral joints). Further longitudinal X-ray follow-up to 2 years of the PSUMMIT I population with a pre-defined statistical analysis plan would be required before that additional claim can be made. At this stage, a statistically significant inhibition of structural damage progression after 24 weeks of treatment with USK in subjects with active PsA has only been observed in the anti-TNF naïve cohort of PSUMMIT I and the result has not been replicated in the accompanying PSUMMIT II trial.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies (PSUMMIT I and II), the following safety data was collected:

- General adverse events (AEs) were assessed by completion of the AE Case Report Form (CRF) and physical examination assessments every 4 weeks for the initial 28 weeks of treatment follow-up, and then every 12 weeks thereafter.
- AEs of particular interest including local injection site reactions (ISR), hypersensitivity reactions, infections (overall and serious), cardiovascular events, neurologic disorders, rebound of skin psoriasis and malignancies were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests including haematology, biochemistry and urinalysis were performed at baseline and every 4 weeks until Week 28, and then every 12 weeks thereafter.
- Screening tests for tuberculosis (Chest X-ray and QuantiFeron Gold testing; or PPD skin testing in countries without QuantiFeron Gold testing) were taken at baseline and a tuberculosis questionnaire was performed every 4 weeks until Week 28, and then every 12 weeks thereafter.
- Vital signs such as blood pressure, heart rate, weight and temperature were performed at each scheduled study visit.
- Serum for anti-USK antibodies was collected at baseline, Week 24 and Weeks 52 - 60.

In both Phase III studies, the focus of the safety presentation was on the placebo-controlled period through to Week 16 because this allowed a direct comparison across randomised treatment groups prior to early escape. Analyses were also performed on data through to Week 24 in both studies (that is, the mandatory placebo to USK treatment crossover time point) as well as for data up to Week 52 in PSUMMIT I and up to Week 60 in PSUMMIT II. When comparing the rates of AEs after Week 16 in both trials, the interpretation of the findings is clouded as subjects may no longer be receiving their initial randomised treatment (due to early escape or crossover), and the number of subjects as well as lengths of treatment follow-up differed between the groups.

AEs were summarised by the MedDRA classification using System Organ Class (SOC) and Preferred Term (PT) nomenclature.

8.1.2. Pivotal studies that assessed safety as a primary outcome

No studies in the USK PsA program assessed safety as the primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

No dose-response study was provided in the submission. Study C0743T10 was a non-pivotal, Phase II trial that provided safety data on general AEs, AEs of special interest (for example, injection site reactions), blood parameters (haematology and clinical chemistry), physical examination and anti-drug antibodies. The study report included in this submission contains safety data collected through to 36 weeks of follow-up.

8.1.4. Other studies evaluable for safety only

The submission also contained summary safety data from clinical studies in the approved indication of psoriasis (a total of 4 studies in which 3117 subjects received at least 1 dose of USK; treatment follow-up for up to 5 years) and 2 Phase II studies in Crohn's disease. The studies were provided for summary comparative purposes and did not reveal any significant differences in the incidence and type of AEs according to underlying treatment indication.

8.2. Patient exposure

Up to the end of the current reporting period for each of the 3 PsA studies, a total of 914 subjects have received treatment with USK. Of these subjects, 75.7% (692 subjects) have been exposed to USK for at least 6 months, and 23.3% (213 subjects) have been exposed for at least 1 year – refer to Table 25. In the combined PsA dataset, more than 300 subjects have been exposed to both proposed doses of USK (45 and 90 mg) for at least 6 months. The median exposed dose in the USK 45 mg group is 135 mg, and the median exposed dose in the 90 mg cohort is 270 mg. During the placebo-controlled phases of all 3 PsA trials (up to Week 16 for the PSUMMIT studies and up to Week 12 in Study C0743T10), the average duration of follow-up and treatment exposure were comparable between the placebo and USK treatment groups. After the placebo-controlled periods, the average duration of follow-up and average duration of exposure were lower for subjects in the control groups than for subjects in the USK treatment arms.

In this submission, the sponsor also presented summaries of safety data from other treatment indications (psoriasis and Crohn's disease) in support of the PsA safety data. Some of this data has already been evaluated by the TGA as part of obtaining a treatment indication in psoriasis. There are 4 psoriasis trials, which have followed patients for up to 5 years. In the psoriasis studies, a total of 1168 subjects have been exposed to USK 45 mg and 1438 subjects have received USK 90 mg for at least 6 months. In terms of long-term safety, 307 subjects in the 45 mg group and 432 subjects in the 90 mg cohort have received USK for at least 5 years. USK has also been evaluated in 2 Phase II trials in Crohn's disease (C0379T07 and C0743T26). A total of 158 subjects (26.4% of 599) were exposed to USK for at least 6 months with intravenous doses up to 6 mg/kg.

Table 25: Summary of USK Exposure in Psoriatic Arthritis Studies and Other Indications.

	PsA Studies[b]			Psoriasis Studies[c]			Crohn's Disease Studies[d]
	45 mg	90 mg	Combined	45 mg	90 mg	Combined	Combined Ustekinumab
Subjects treated with ustekinumab[a]	473	497	914	1319	2001	3117	599
Duration of ustekinumab exposure							
At least 6 months[e]	345 (72.9%)	309 (62.2%)	692 (75.7%)	1168 (88.6%)	1438 (71.9%)	2414 (77.4%)	158 (26.4%)
At least 1 year[f]	88 (18.6%)	108 (21.7%)	213 (23.3%)	901 (68.3%)	1136 (56.8%)	1855 (59.5%)	0
At least 18 months[g]	0	0	0	808 (61.3%)	1025 (51.2%)	1697 (54.4%)	0
At least 2 years[h]	0	0	0	713 (54.1%)	986 (49.3%)	1653 (53.0%)	0
At least 3 years[h]	0	0	0	617 (46.8%)	886 (44.3%)	1569 (50.3%)	0
At least 4 years[h]	0	0	0	566 (42.9%)	746 (37.3%)	1482 (47.5%)	0
At least 5 years[h]	0	0	0	307 (23.3%)	432 (21.6%)	838 (26.9%)	0
Avg number of ustekinumab administrations	3.2	3.3	3.4	13.6	12.4	13.7	2.0
Total dose (mg)							
N	473	497	914	1319	2001	3117	599
Mean (SD)	143.1 (48.39)	274.3 (113.51)	223.2 (107.30)	611.0 (430.93)	1116.7 (921.81)	975.4 (845.62)	331.8 (163.20)
Median	135.0	270.0	225.0	540.0	810.0	810.0	360.0
IQ range	(90.0; 180.0)	(252.0; 360.0)	(135.0; 270.0)	(180.0; 990.0)	(180.0; 1980.0)	(180.0; 1800.0)	(236.7; 379.8)
Range	(45; 270)	(63; 450)	(45; 450)	(45; 1395)	(45; 2880)	(45; 2880)	(42; 1035)

[a] PsA studies include C0743T10, CNTO1275PSA3001, and CNTO1275PSA3002. Psoriasis studies include C0379T04, C0743T08, C0743T09, and C0743T12. Crohn's disease studies include C0379T07 and C0743T26.
[b] Placebo crossover subjects were included in the ustekinumab columns after crossover to ustekinumab. For C0743T10, subjects who were randomized to ustekinumab were included in 90 mg column. For CNTO1275PsA3001 and CNTO1275PsA3002, subjects who were dose escalated from 45 mg to 90 mg were switched to the 90 mg column following dose escalation.
[c] Placebo crossover subjects and etanercept crossover subjects were included in the ustekinumab columns after crossover to ustekinumab. For C0743T09, subjects who were dose escalated from 45 mg to 90 mg were switched to the corresponding column following dose escalation.
[d] Placebo crossover subjects were included in the ustekinumab column after crossover to ustekinumab
[e] The duration between the first and last ustekinumab administration was at least 14 weeks.
[f] The duration between the first and last ustekinumab administration was at least 38 weeks.
[g] The duration between the first and last ustekinumab administration was at least 62 weeks.
[h] At least 2 years: The duration between the first and last ustekinumab administration was at least 88 weeks. At least 3 years: The duration between the first and last ustekinumab administration was at least 140 weeks. At least 4 years: The duration between the first and last ustekinumab administration was at least 192 weeks. At least 5 years: The duration between the first and last ustekinumab administration was at least 240 weeks.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

8.3.1.1.1. PSUMMIT I

8.3.1.1.1.1. Up to week 16 (placebo-controlled period)

Up to Week 16, the proportions of subjects experiencing at least 1 AE were similar in the in the USK 45 mg group (39.5%; 81/205), USK 90 mg arm (43.1%; 88/204) and placebo group (43.4%; 89/205). In addition, the individual types of AEs were similar between the placebo and both USK treatment groups. The SOC with the most frequently reported AEs was infections and infestations, which occurred in similar proportions of subjects in the placebo, USK 45 mg and USK 90 mg arms (20.5%, 16.6% and 20.1%, respectively). Musculoskeletal and connective tissue disorders was the second most frequent SOC with a higher proportion of these AEs in the placebo group (11.2%) compared with the USK-treated subjects (5.4% in the 45 mg group and 8.8% in the 90 mg group). Gastrointestinal disorders were the third most frequent SOC with higher proportions in the USK-treated subjects (6.8% in the 45 mg group and 6.9% in the 90 mg arm) compared with the placebo group (3.4%). Table 26 lists the AEs recorded (presented by PT) in at least 1% of subjects. Nasopharyngitis as the most frequently reported AE occurring at an incidence of 3.9% in both the placebo and USK 45 mg groups versus 5.4% in the USK 90 mg arm. The proportions of subjects reporting individual AE types (by PT) were generally comparable between the combined USK cohort and the control group with the exception of the following: headache (3.4% in the combined USK group versus 1.0% in the placebo group), nausea (2.4% in the combined USK group versus 0% in the placebo group), diarrhoea (2.2% in the combined USK group versus 0% in the placebo group), active PsA (1.0% in the combined USK group versus 3.4% in the placebo group) and sinusitis (1.0% in the combined USK group versus 2.9% in the placebo group).

Concurrent MTX use, age and gender did not appear to influence the frequency or pattern of AEs with USK therapy. However, subjects weighing > 100 kg (versus those weighing ≤ 100 kg) had a higher frequency of overall AEs, as well as infection related AEs and study discontinuations due to AEs, regardless of study treatment assignment (placebo and both USK doses) – refer to Table 27.

Table 26: Subjects with Adverse Events by Preferred Term up to Week 16 in PSUMMIT I Study.

		Ustekinumab		
	Placebo	45 mg	90 mg	Combined
Subjects treated	205	205	204	409
Avg duration of follow-up (weeks)	16.16	16.21	16.04	16.13
Subjects Treated	205	205	204	409
Avg exposure (number of administrations)	1.99	1.99	1.97	1.98
Total number of subjects with adverse events	91 (44.4%)	84 (41.0%)	89 (43.6%)	173 (42.3%)
Preferred terms				
Nasopharyngitis	8 (3.9%)	8 (3.9%)	11 (5.4%)	19 (4.6%)
Headache	2 (1.0%)	10 (4.9%)	4 (2.0%)	14 (3.4%)
Upper respiratory tract infection	10 (4.9%)	5 (2.4%)	9 (4.4%)	14 (3.4%)
Arthralgia	3 (1.5%)	4 (2.0%)	6 (2.9%)	10 (2.4%)
Nausea	0	4 (2.0%)	6 (2.9%)	10 (2.4%)
Diarrhoea	0	5 (2.4%)	4 (2.0%)	9 (2.2%)
Hypertension	4 (2.0%)	2 (1.0%)	6 (2.9%)	8 (2.0%)
Alanine aminotransferase increased	3 (1.5%)	3 (1.5%)	3 (1.5%)	6 (1.5%)
Cough	5 (2.4%)	5 (2.4%)	1 (0.5%)	6 (1.5%)
Pruritus	0	3 (1.5%)	3 (1.5%)	6 (1.5%)
Abdominal pain	0	2 (1.0%)	3 (1.5%)	5 (1.2%)
Fatigue	3 (1.5%)	1 (0.5%)	4 (2.0%)	5 (1.2%)
Oropharyngeal pain	2 (1.0%)	3 (1.5%)	2 (1.0%)	5 (1.2%)
Depression	2 (1.0%)	0	4 (2.0%)	4 (1.0%)
Dyspepsia	3 (1.5%)	4 (2.0%)	0	4 (1.0%)
Gastroenteritis	1 (0.5%)	2 (1.0%)	2 (1.0%)	4 (1.0%)
Influenza	0	2 (1.0%)	2 (1.0%)	4 (1.0%)
Insomnia	0	1 (0.5%)	3 (1.5%)	4 (1.0%)
Nasal congestion	2 (1.0%)	4 (2.0%)	0	4 (1.0%)
Pain in extremity	2 (1.0%)	1 (0.5%)	3 (1.5%)	4 (1.0%)
Psoriatic arthropathy	7 (3.4%)	0	4 (2.0%)	4 (1.0%)
Sinusitis	6 (2.9%)	2 (1.0%)	2 (1.0%)	4 (1.0%)

Table 27: Adverse Events by Subject Weight (≤ 100 kg versus > 100 kg) up to Week 16 in PSUMMIT I and PSUMMIT II Studies (combined dataset).

	Placebo	45 mg	Ustekinumab 90 mg	Combined
Weight (kg)				
≤ 100				
N	227	227	227	454
Avg duration of follow-up (weeks)	15.69	16.18	15.96	16.07
Subjects with 1 or more adverse events	102 (44.9%)	106 (46.7%)	102 (44.9%)	208 (45.8%)
Subjects with 1 or more serious adverse events	8 (3.5%)	2 (0.9%)	3 (1.3%)	5 (1.1%)
Subjects with 1 or more infections	46 (20.3%)	43 (18.9%)	46 (20.3%)	89 (19.6%)
Subjects who discontinued study agent because of 1 or more adverse events	6 (2.6%)	1 (0.4%)	3 (1.3%)	4 (0.9%)
> 100				
N	82	81	81	162
Avg duration of follow-up (weeks)	16.09	16.06	16.13	16.09
Subjects with 1 or more adverse events	46 (56.1%)	43 (53.1%)	50 (61.7%)	93 (57.4%)
Subjects with 1 or more serious adverse events	1 (1.2%)	2 (2.5%)	1 (1.2%)	3 (1.9%)
Subjects with 1 or more infections	22 (26.8%)	21 (25.9%)	20 (24.7%)	41 (25.3%)
Subjects who discontinued study agent because of 1 or more adverse events	5 (6.1%)	2 (2.5%)	1 (1.2%)	3 (1.9%)

8.3.1.1.1.2. Up to week 24

Up to Week 24, 54.1% (111/205) of the subjects in the USK 45 mg group, 52.0% (106/204) of the patients in the USK 90 mg arm and 49.8% (102/205) of the subjects in the placebo group experienced at least 1 AE. A similar proportion (49.5%) of subjects in the combined USK group (which includes placebo-treated subjects who escaped to USK at Week 16) had 1 or more AEs versus 50.7% of subjects who remained in the placebo treatment arm until Week 24. Overall, this does not represent a disproportional increase in AEs occurring after Week 16 as this includes a longer duration of treatment in all of the groups. The SOC with the most frequently reported AEs remained infections and infestations occurring in 27.8% of the combined USK 45 mg group (includes placebo escape patients) and 27.9% of the USK 90 mg group. Nasopharyngitis was the most frequently (≥ 5% incidence) reported AE with a frequency of 6.3% in the combined USK 45 mg group, 7.4% in the USK 90 mg arm and 4.4% in the placebo group. Gastrointestinal disorders (mainly diarrhoea) were also common affecting 5.4% of patients in the combined USK 45 mg group, 2.0% of subjects in the USK 90 mg arm and 0% of patients in the placebo group.

8.3.1.1.1.3. Up to week 52

Up until Week 52, the durations of follow-up and exposure to USK were similar in the combined 45 mg (51 weeks, 4.77 administrations) and 90 mg groups (50 weeks, 4.77 administrations). At this time point, 69.2% of the subjects in the USK 45 mg group and 64.4% of the subjects in the USK 90 mg arm experienced at least 1 AE. The overall incidence of AEs at Week 52 compared to Week 24 does not represent a disproportional increase in AEs after Week 24. A similar type and pattern of AEs was observed through to Week 52 as identified at Week 24. Up to Week 52, the SOC with the most frequently reported AEs remained infections and infestations (45.0% in the combined USK 45 mg group and 44.1% in the USK 90 mg arm. Nasopharyngitis and URTI (Upper Respiratory Tract Infection) remained the most frequently reported AEs by PT with similar proportions in the combined USK 45 mg (14.2% and 9.2%, respectively) and USK 90 mg (13.6% and 8.5%, respectively) treatment groups.

At all time points of safety assessment (Weeks 16, 24 and 52), the use of concurrent MTX did not appear to affect the incidence of AEs (overall and infection related). However, subjects with

a body weight of > 100 kg (versus those ≤ 100 kg) had a consistently higher incidence of overall and infection related AEs, regardless of whether or not they received USK or placebo.

8.3.1.1.2. PSUMMIT II

8.3.1.1.2.1. Up to week 16 (placebo-controlled period)

Through to Week 16, the proportions of subjects experiencing at least 1 AE was slightly less in the placebo group (54.8%; 57/104) compared to the 2 USK treatment arms (63.1% [65/103] in the 45 mg dose arm and 60.6% [63/104] in the 90 mg treatment groups) despite similar overall periods of exposure – refer to Table 28. Infection and infestations was the SOC with the most frequently reported AEs reported in 23.1% of subjects in the control arm versus 28.2% of patients in the USK 45 mg group and 26.0% of subjects in the USK 90 mg arm. The most commonly reported AEs in this SOC were nasopharyngitis (4.8% in the placebo group versus 7.8% in the USK 45 mg arm and 9.6% in the USK 90 mg group) and URTI (3.8% in the placebo group versus 4.9% in the USK 45 mg cohort and 2.9% in the USK 90 mg group). Following nasopharyngitis, the next most commonly reported AEs overall were headache (3.8% in the placebo group versus 4.9% in the USK 45 mg arm and 4.8% in the USK 90 mg group) and arthralgia (1.0% in the placebo arm versus 4.9% in the USK 45 mg group and 3.8% in the USK 90 mg arm). The proportion of subjects reporting these individual events (by PT) were generally comparable between the combined USK group and the placebo arm with the exception of the following PTs for which a difference of at least 2% was seen between the combined USK group and the placebo group: nasopharyngitis (8.7% for combined USK versus 4.8% in the placebo group), fatigue (3.4% for combined USK versus 0 in control), back pain (2.4% for combined USK versus 0 for placebo) and oropharyngeal pain (2.4% for combined USK versus 0 for placebo). All 4 of these AEs are known to be associated with USK and appear in the current PI as potential AEs. Interestingly, the proportion of subjects who reported arthralgia as an AE was higher in the combined USK group (4.3%) compared with the placebo group (1.0%), but the opposite was true for the proportion of subjects reporting active PsA (2.4% in the combined USK group compared with 4.8% in the placebo group).

Table 28: Subjects with Adverse Events by Preferred Term up to Week 16 in PSUMMIT II Study

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Combined
Subjects treated	104	103	104	207
Avg duration of follow-up (weeks)	15.08	16.02	15.94	15.98
Avg exposure (number of administrations)	1.90	1.98	1.99	1.99
Total number of subjects with adverse events	57 (54.8%)	65 (63.1%)	63 (60.6%)	128 (61.8%)
Preferred terms				
Nasopharyngitis	5 (4.8%)	8 (7.8%)	10 (9.6%)	18 (8.7%)
Headache	4 (3.8%)	5 (4.9%)	5 (4.8%)	10 (4.8%)
Arthralgia	1 (1.0%)	5 (4.9%)	4 (3.8%)	9 (4.3%)
Upper respiratory tract infection	4 (3.8%)	5 (4.9%)	3 (2.9%)	8 (3.9%)
Fatigue	0	5 (4.9%)	2 (1.9%)	7 (3.4%)
Nausea	2 (1.9%)	4 (3.9%)	3 (2.9%)	7 (3.4%)
Back pain	0	1 (1.0%)	4 (3.8%)	5 (2.4%)
Diarrhoea	3 (2.9%)	4 (3.9%)	1 (1.0%)	5 (2.4%)
Oropharyngeal pain	0	4 (3.9%)	1 (1.0%)	5 (2.4%)
Psoriasis	3 (2.9%)	4 (3.9%)	1 (1.0%)	5 (2.4%)
Psoriatic arthropathy	5 (4.8%)	4 (3.9%)	1 (1.0%)	5 (2.4%)
Alanine aminotransferase increased	0	1 (1.0%)	3 (2.9%)	4 (1.9%)
Injection site pain	0	2 (1.9%)	2 (1.9%)	4 (1.9%)
Oedema peripheral	4 (3.8%)	2 (1.9%)	2 (1.9%)	4 (1.9%)
Sinusitis	3 (2.9%)	1 (1.0%)	3 (2.9%)	4 (1.9%)
Abdominal pain upper	1 (1.0%)	1 (1.0%)	2 (1.9%)	3 (1.4%)
Hypertension	1 (1.0%)	3 (2.9%)	0	3 (1.4%)
Influenza	1 (1.0%)	2 (1.9%)	1 (1.0%)	3 (1.4%)
Injection site erythema	0	1 (1.0%)	2 (1.9%)	3 (1.4%)
Oral herpes	1 (1.0%)	2 (1.9%)	1 (1.0%)	3 (1.4%)
Abdominal pain	0	1 (1.0%)	1 (1.0%)	2 (1.0%)
Aspartate aminotransferase increased	0	0	2 (1.9%)	2 (1.0%)
C-reactive protein increased	0	1 (1.0%)	1 (1.0%)	2 (1.0%)
Cataract	0	0	2 (1.9%)	2 (1.0%)
Chest pain	0	1 (1.0%)	1 (1.0%)	2 (1.0%)
Confusion	0	1 (1.0%)	1 (1.0%)	2 (1.0%)
Cough	1 (1.0%)	2 (1.9%)	0	2 (1.0%)
Dizziness	1 (1.0%)	2 (1.9%)	0	2 (1.0%)
Dry eye	0	2 (1.9%)	0	2 (1.0%)
Erythema	2 (1.9%)	2 (1.9%)	0	2 (1.0%)
Fungal skin infection	1 (1.0%)	0	2 (1.9%)	2 (1.0%)
Joint swelling	0	0	2 (1.9%)	2 (1.0%)
Liver function test abnormal	1 (1.0%)	1 (1.0%)	1 (1.0%)	2 (1.0%)
Lower respiratory tract infection	0	0	2 (1.9%)	2 (1.0%)
Muscle spasms	0	0	2 (1.9%)	2 (1.0%)
Myalgia	0	1 (1.0%)	1 (1.0%)	2 (1.0%)
Otitis externa	0	1 (1.0%)	1 (1.0%)	2 (1.0%)
Otitis media	0	0	2 (1.9%)	2 (1.0%)
Pain	1 (1.0%)	2 (1.9%)	0	2 (1.0%)
Pain in extremity	0	0	2 (1.9%)	2 (1.0%)
Paraesthesia	0	1 (1.0%)	1 (1.0%)	2 (1.0%)
Rash	1 (1.0%)	1 (1.0%)	1 (1.0%)	2 (1.0%)
Respiratory tract infection viral	1 (1.0%)	2 (1.9%)	0	2 (1.0%)
Rhinitis allergic	0	2 (1.9%)	0	2 (1.0%)
Sciatica	1 (1.0%)	2 (1.9%)	0	2 (1.0%)
Syncope	0	0	2 (1.9%)	2 (1.0%)
Thrombocytopenia	0	2 (1.9%)	0	2 (1.0%)
Tooth infection	1 (1.0%)	1 (1.0%)	1 (1.0%)	2 (1.0%)
Vomiting	2 (1.9%)	1 (1.0%)	1 (1.0%)	2 (1.0%)
Vulvovaginal mycotic infection	0	1 (1.0%)	1 (1.0%)	2 (1.0%)
Wound	0	1 (1.0%)	1 (1.0%)	2 (1.0%)

8.3.1.1.2.2. Up to week 24

Up to Week 24, 70.9% (73/103) of the subjects in the combined USK 45 mg group, 69.2% (72/104) of the patients in the USK 90 mg arm and 63.5% (66/104) of the subjects in the placebo group experienced at least 1 AE. A similar proportion (66.4%; 158/238) of subjects in the combined USK group (which includes placebo-treated subjects who escaped to USK at Week 16) had 1 or more AEs versus 63.5% of subjects who remained in the placebo treatment arm until Week 24. This does not represent a disproportional increase in AEs occurring after Week 16 as this includes a longer duration of treatment in all of the groups (average duration of follow-up was 19.4 weeks in the placebo group and 21.6 weeks in the combined USK cohort). The SOC with the most frequently reported AEs remained infections and infestations occurring

in 41.7% of the combined USK 45 mg group (includes placebo escape patients) and 35.6% of the USK 90 mg group. Nasopharyngitis was the most frequently (≥ 5% incidence) reported AE with a frequency of 9.7% in the combined USK 45 mg group, 12.5% in the USK 90 mg arm and 7.7% in the placebo group. Gastrointestinal disorders (mainly nausea and diarrhoea) were also common affecting 11.7% of patients in the combined USK 45 mg group, 14.4% of subjects in the USK 90 mg arm and 12.5% of patients in the placebo group.

8.3.1.1.2.3. Up to week 60

Up until Week 60, the durations of follow-up and exposure to USK were similar in the combined 45 mg (54 weeks, 4.61 administrations) and 90 mg groups (53 weeks, 4.53 administrations). At this time point, 78.6% (81/103) of the subjects in the USK 45 mg group and 77.9% (81/104) of the subjects in the USK 90 mg arm experienced at least 1 AE. The overall incidence of AEs at Week 60 compared to Week 24 does not represent a disproportional increase in AEs after Week 24. A similar type and pattern of AEs was observed through to Week 60 as identified at Week 24. Up to Week 60, the SOC with the most frequently reported AEs remained infections. Nasopharyngitis and URTI remained the most frequently reported AEs by PT with similar proportions in the combined USK 45 mg (14.6% and 11.7%, respectively) and USK 90 mg (19.2% and 9.6%, respectively) treatment groups.

At all time points of safety assessment (Weeks 16, 24 and 60), the use of concurrent MTX and prior anti-TNF exposure did not appear to affect the incidence of AEs (overall and infection related). However, female subjects and those with a body weight of > 100 kg (versus those ≤ 100 kg) had a consistently higher incidence of overall and infection related AEs, as well as study discontinuation due to AEs, regardless of whether or not they received USK or placebo – refer to Table 27 for data up to Week 16 (placebo-controlled period).

8.3.1.1.3. Other studies

Up until Week 12 in Study C0743T10, the proportions of subjects reporting at least 1 AE were comparable in the placebo (62.9%; 44/70) and USK treatment groups (60.5%; 46/76). The most frequently reported AE by SOC was infections and infestations reported by 28.6% (20/70) of subjects in the placebo group and 31.6% (24/76) of subjects in the USK arm. Across all of the SOC categories, the proportions of subjects reporting AEs through to Week 12 were comparable between the 2 treatment groups. The most frequently reported AEs (≥ 5% of subjects in either treatment group) by PT through to Week 12 were URTI (8.6% in the control group and 13.2% in the USK arm), nasopharyngitis (2.9% in the control arm and 10.5% in the USK group), diarrhoea (2.9% in the placebo group and 6.6% in the USK arm), headache (5.7% in the control arm and 6.6% in the USK group) and influenza (5.7% in the placebo group and 1.3% in the USK arm).

Up until Week 36 in Study C0743T10, 76.3% (58/76) of subjects in the USK group and 63.2% (36/57) of subjects in the placebo to USK crossover arm reported an AE. The pattern of AEs through to Week 36 was generally similar to that reported up until Week 12. The most frequently reported type of AEs by SOC was infections and infestations. The most frequently reported individual type of AEs (≥ 5% of subjects in the USK combined group) was URTI (14.3%), nasopharyngitis (9.8%), diarrhoea (6.8%), headache (5.3%) and sinusitis (5.3%).

Study C0743T10 also did subgroup analyses of the incidence and pattern of AEs. The use of concomitant MTX did not alter the frequency or pattern of AEs. However, subject weight > 90 kg and past biologic treatment exposure predicted an increased incidence of overall AEs (regardless of treatment – observed in both placebo and USK treated patients) but no specific types of AEs. These are known risk factors for infection and other AEs, and the observation is within expectations.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies

8.3.2.1.1. PSUMMIT I

In this trial, treatment related AEs (that is, reasonably related according to site investigator) were only summarised up to Week 24. A similar proportion of subjects in the USK 45 mg group (19.5%) and USK 90 mg arm (18.1%) experienced at least 1 treatment related AE up until Week 24 compared with 16.1% of subjects in the placebo group. No significant difference in the type of treatment related AEs was identified between the USK groups and placebo.

Through to Week 16, the proportion of subjects experiencing at least 1 infection was comparable across the treatment groups affecting 21.0% (43/205) of subjects in the placebo group, 16.6% (34/205) of patients in the USK 45 mg arm and 19.6% (40/204) of subjects in the USK 90 mg group. The most commonly reported type of infection was nasopharyngitis followed by URTI. Consistent with Week 16 results, the proportion of subjects in the USK groups reporting 1 or more infections through to Week 24 was 26.8% in the combined USK 45 mg group and 27.0% in the USK 90 mg arm. Given the increased exposure to therapy (mean 22 weeks), this does not represent disproportional increase compared with the Week 16 results. Through to Week 52, 42.5% of the subjects in the combined USK 45 mg group and 42.4% of the subjects in the USK 90 mg arm experienced at least 1 infection. The types of infections observed through to Week 24 and 52 were generally similar to those seen up to Week 24 with nasopharyngitis (11 - 12.5% incidence) and URTI (8.5 - 9.2% incidence) continuing to be the most frequently reported infections in USK treated subjects (either dose).

By 24 weeks, the total number of subjects with ISRs was 1.5% (7/468) for the combined USK injection group and 1.5% (9/614) in the placebo injection group. The most commonly reported AE to either placebo or USK injections was injection site erythema, and of these AEs were considered mild by the investigator. No subjects discontinued due to ISR.

8.3.2.1.2. PSUMMIT II

Like the PSUMMIT I trial, this study only recorded treatment related AEs up to Week 24. A similar proportion of subjects in the USK 45 mg group (22.3%; 23/103) and USK 90 mg arm (26.0%; 27/104) experienced at least 1 treatment related AE up until Week 24 compared with 21.2% (22/104) of subjects in the placebo group. No significant difference in the type of treatment related AEs was identified between the USK groups and placebo.

Through to Week 16, the proportion of subjects experiencing at least 1 infection was comparable across the treatment groups affecting 24.0% (25/104) of subjects in the placebo group, 29.1% (30/103) of patients in the USK 45 mg arm and 25.0% (26/104) of subjects in the USK 90 mg group. The most commonly reported type of infection was nasopharyngitis followed by URTI. Consistent with Week 16 results, the proportion of subjects in the USK groups reporting 1 or more infections through to Week 24 was 40.8% (42/103) in the combined USK 45 mg group and 34.6% (36/104) in the USK 90 mg arm. Given the increased exposure to therapy (mean 21.6 weeks), this does not represent disproportional increase compared with the Week 16 results. Through to Week 60, 52.4% of the subjects in the combined USK 45 mg group and 54.8% of the subjects in the USK 90 mg arm experienced at least 1 infection. The types of infections observed through to Week 24 and 60 were generally similar to those seen up to Week 24 with nasopharyngitis (11 - 12.5% incidence) and URTI (8.0 - 10.7% incidence) continuing to be the most frequently reported infections in USK treated subjects (either dose).

By 24 weeks, the total number of subjects with ISRs was 2.5% (6/238) for the combined USK injection group and 1.6% (5/311) in the placebo injection group. The most commonly reported AEs to either placebo or USK injections was injection site erythema and injection site pain, and of these AEs were considered mild by the investigator. No subjects discontinued due to ISR.

8.3.2.2. Other studies

The report for Study C0743T10 did not present AE data according to relationship to treatment, however, AEs of special interest such as infections, ISRs and psoriasis rebound (defined as new erythrodermic or pustular psoriasis, or a PASI of ≥ 125% of the baseline PASI, occurring within 3 months of the last USK administration) were considered.

In the placebo controlled period (first 12 weeks) of Study C0743T10, infections (as classified by the site investigator) were reported in 30.0% (21/70) of subjects in the placebo group and 35.5% (27/76) of subjects in the USK arm. The incidence of URTI, diarrhoea and nasopharyngitis were higher in the USK group, while the incidence of influenza was higher in the placebo group. Between Weeks 12 and 36, treatment-emergent infections were reported by 55.3% (42/76) of subjects in the USK group and by 35.1% (20/57) of subjects in the placebo to USK crossover arm. Similar to the data observed through to Week 12, the most commonly reported infections were URTI, nasopharyngitis and diarrhoea. Through to Week 36, infections requiring oral or parenteral antimicrobial treatment were reported by 17.5% of subjects in the placebo to USK crossover group and 25.0% of subjects in the USK group.

Study medicine injections were well tolerated, and the proportion of subjects experiencing 1 or more injection-site reactions was low. Up to Week 12, 3 subjects (3.9% of 76) reported at least 1 injection-site reaction to USK and all were mild or moderate. No subjects reported injection-site reactions to placebo. After Week 12 and through to Week 36, 2 additional subjects reported at least 1 mild injection-site reaction to USK, and no subjects reported injection-site reactions to placebo. No severe injection-site reactions, anaphylactic reactions or serum sickness-like reactions following drug administration were observed in Study C0743T10 through to Week 36.

One subject in the placebo to USK crossover group met the criteria for psoriasis rebound by reporting a PASI ≥ 125% or greater of baseline within 3 months of the last USK administration. The patient had a PASI score of 12.8 at baseline, and never achieved a PASI 50 response.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal studies

8.3.3.1.1. PSUMMIT I

No deaths, malignancies, opportunistic infections or major neurological disorders were reported up to 52 weeks in the safety population of the PSUMMIT I Study.

Up to Week 16, the proportion of subjects experiencing at least 1 SAE was low and similar across the treatment groups affecting 2.0% (4/205) of subjects in the placebo group, 2.0% (4/205) of patients in the USK 45 mg arm and 1.5% (3/204) in the USK 90 mg group. No SAE occurred in more than 1 subject. One SAE of angina pectoris was reported in a placebo-treated subject. The types of SAEs reported in USK treated subjects were erythrodermic psoriasis, depression and cholecystitis (all in the 90 mg group); and duodenitis, acute renal failure (considered reasonably related), spinal compression fracture and cervical polyp (in the USK 45 mg arm).

Consistent with results through to Week 16, the proportion of subjects experiencing SAEs at or before Week 24 in the PSUMMIT I Study remained low – 2.9% of subjects in the combined USK 45 mg group (including early escape patients from the placebo arm) and 1.5% of patients in the 90 mg dose group. The additional SAEs occurring between Weeks 16 and 24 included another case of erythrodermic psoriasis occurring in a patient who escaped from placebo to USK 45 mg injections.

Through to Week 52, 5.8% of subjects in the combined USK 45 mg group and 2.5% of patients in the USK 90 mg arm experienced at least 1 SAE, which does not reflect a significant increase in the incidence of SAEs given the extended drug exposure period (mean of 44 weeks of treatment follow-up). Up to Week 24, there were no subjects who reported serious infections. Four

subjects reported serious infections in the Week 52 safety subset: 1 patient with pharyngolaryngeal abscess (USK 90 mg group), 1 subject with salpingitis (USK 45 mg group who did not early escape), and 2 subjects with acute cholecystitis (1 subject in the USK 45 mg group who did not early escape and the other patient in the placebo → USK 45 mg group who crossed over to receive USK at Week 24).

Regarding major adverse cardiovascular events, 1 SAE of angina pectoris was reported in a placebo-treated subject through to Week 16. After the placebo-controlled period (between Weeks 16 and 24), another subject (in the USK 45 mg group) suffered a cerebrovascular accident. Through to Week 52, 2 subjects in the placebo → USK 45 mg group experienced serious cardiovascular events and discontinued study medicine. One subject experienced atrial fibrillation and hypertension on Day 194 of the study after receiving their last dose of USK on Day 169. The other patient suffered a myocardial infarction on Study Day361 after receiving their last dose of USK on Day 281.

Up to Week 24, there were 3 pregnancies reported in treated subjects (1 was in the USK 90 mg group and 2 in the placebo arm), as well as 1 partner pregnancy for a subject in the USK 45 mg group. The 3 subjects discontinued from the study per protocol. No abnormal outcomes were reported.

8.3.3.1.2. PSUMMIT II

No deaths were reported in the PSUMMIT II Study through to Week 60. A total of 2 patients developed malignancy. One subject treated with USK 90 mg injections had squamous cell carcinoma in an area of cleared plaque psoriasis (onset Study Day22). As per the trial protocol, treatment with study drug was withdrawn. Another patient was reported as having breast cancer identified on Study Day215, and subsequently withdrew from the trial. This patient was in the placebo group and had switched to USK 45 mg therapy at Week 24. Both patients had prior exposure to anti-TNF medicines. No neurologic disorders (such as demyelination or reversible posterior leukoencephalopathy syndrome) were recorded through to 60 weeks.

Up to Week 16, the proportion of subjects experiencing at least 1 SAE was low but higher in the placebo arm (4.8%; 5/104) compared to the USK treatment groups (0 in the USK 45 mg arm and 1.0% [1/104] in the USK 90 mg group). The SAE occurring in the USK treated subject was syncope and acute renal injury (onset Study Day14; considered likely to be due to concurrent NSAID use and dehydration). Through to Week 24, 1 additional subject in the USK 90 mg group experienced an SAE (arthritis) and placebo-treated patient who entered early escape to USK 45 mg reported suicidal ideation. None of the SAEs through to Week 24 were considered to be treatment related. Through to Week 60, 5.8% of subjects in each of the combined USK 45 mg and 90 mg groups experienced at least 1 SAE, which does not reflect a significant increase in the incidence of SAEs given the extended drug exposure period (mean of 54 weeks of treatment follow-up).

Up to Week 24, only 1 subject (in the placebo arm) recorded a serious infection – interstitial lung disease complicated by bilateral pneumonia. Two subjects (both treated with USK 90 mg injections) reported serious infections between Weeks 24 and 60. One patient (50 year old male) developed methicillin-sensitive Staphylococcal bacteraemia, believed to have originated from a psoriatic plaque infection in the skin overlying the knee. The other subject experienced septic shock and had Candida species cultured from the faeces but not blood. Both subjects also had a history of prior anti-TNF exposure. No subjects recorded active TB or serious opportunistic infection up to 60 weeks.

No investigator-reported, major adverse cardiovascular events were reported in any treatment group through to Week 24. Two non-serious events of tachycardia were reported in the cardiac disorders SOC before Week 24 affecting 1 subject each in the placebo and USK 90 mg groups. However, between Weeks 24 and 60, 3 subjects experienced myocardial infarction, 2 of which were in the original USK 45 mg group and 1 was receiving treatment with USK 90 mg injections

from baseline. All of the affected individuals had significant risk factors for coronary ischaemia such as prior history of stroke, hypertension, diabetes, smoking and hyperlipidaemia.

Up to Week 60, no pregnancies were reported in treated subjects, and only 1 partner pregnancy for a subject in the placebo to USK 45 mg switch group was observed. The outcome was not reported.

8.3.3.2. Other studies

There were no deaths through to 36 weeks of follow-up in Study C0743T10. Up until 12 weeks, no SAEs were reported in the USK treatment group. Three placebo-treated subjects (4.3% of 70) reported an SAE by Week 12, with 1 report each of myocardial infarction, gastric ulcer haemorrhage, and non-cardiac chest pain. After Week 12 and through to Week 36, SAEs were reported by 7 additional subjects, 1 subject in the placebo group (pelvic mass due to haemorrhagic cyst and scar tissue) who did not cross over to receive USK, and 6 subjects in the USK arm including single reports of myocardial infarction with congestive cardiac failure, abdominal and back pain due to gastric ulcer haemorrhage, haemorrhagic stroke, chest pain, syncope and acute bronchitis. There were no cases of TB or serious opportunistic infection. Only 1 malignancy was reported before 36 weeks. This was a case of recurrent basal cell carcinoma of the skin (week 13) in a 45 year old female who received initial treatment with 4 doses of USK (weeks 0 - 3).

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal studies

8.3.4.1.1. PSUMMIT I

The overall incidence of AEs leading to permanent study medication discontinuation was low in the PSUMMIT I Study. Up to Week 16, a total of 3 (0.7% of 409) subjects in the combined USK group and 3 (1.5% of 205) subjects in the placebo group discontinued study agent due to an AE. Among the 3 subjects in the combined USK group who withdrew due to AEs, 1 subject in the 45 mg group discontinued due to acute renal failure, 1 subject in the 90 mg arm discontinued due to pregnancy (as per study protocol), and 1 subject in the 90 mg group discontinued due to erythrodermic psoriasis. All 3 subjects in the placebo group discontinued due to active PsA.

Through to Week 24, the proportion of subjects that discontinued due to AE remained low across all treatment groups with 1.5% (n = 3) each in the combined USK 45 mg and 90 mg groups and 3.4% (7/204) in the placebo arm. Between Weeks 16 and 24, 2 additional subjects discontinued from the USK 45 mg group (1 subject stopped study treatment due to flank pain and nausea; and the other subject had an ischaemic stroke) and 1 additional subject in the USK 90 mg arm discontinued due to PsA. Four additional placebo arm subjects discontinued between Weeks 16 and 24: 2 due to pregnancy, 1 because of erythrodermic psoriasis and the other due to staphylococcal infection.

At Week 52, an additional 4 subjects discontinued USK due to AEs. One subject in the placebo to USK crossover group suffered myocardial infarction (occurred on Study Day361; last USK injection on Day 281) and another patient in the same cohort developed atrial fibrillation and hypertension (occurred on Day 194; last USK injection on Day 169). The other 2 subjects were in the USK 45 mg group and discontinued due to PsA and salpingitis.

8.3.4.1.2. PSUMMIT II

The overall incidence of AEs leading to permanent study medication discontinuation was low in the PSUMMIT II Study. Up to Week 16, a total of 4 subjects (2 in each dose group; 1.9% of 207) in the combined USK group and 8 (7.7% of 104) subjects in the placebo group discontinued study agent due to an AE. Among the 4 subjects in the combined USK group who withdrew due to AEs, 1 subject in the 45 mg group discontinued due to thrombocytopenia (onset Study Day28 and persisted until withdrawal on Study Day73), 1 subject in the 90 mg arm discontinued due to

squamous cell carcinoma of the skin (as per study protocol), and the other 2 subjects discontinued due to active arthritis. Six of the 8 subjects in the placebo group discontinued due to either active PsA or skin psoriasis.

Through to Week 24, the proportion of subjects that discontinued due to AE remained low across all treatment groups: 1.9% (2 subjects) in the combined USK 45 mg group, 2.9% (3 subjects) in the USK 90 mg arm and 10.6% (11 subjects) in the placebo group. Between Weeks 16 and 24, 1 additional subject discontinued from the USK 90 mg group due to PsA flare.

At Week 60, an additional 2 subjects discontinued USK due to AEs. One subject in the placebo group who escaped to USK 45 mg at Week 16 developed breast cancer and was required to discontinue study medication as per the protocol. Another subject ceased study treatment because of myocardial infarction.

8.3.4.2. Other studies

Up to 12 weeks in Study C0743T10, 4 subjects (5.7% of 70) in the placebo group discontinued due to an AE compared with 1 subject (1.3% of 76) in the USK treatment group. Three of 4 subject discontinuations in the placebo group were primarily due to worsening of underlying psoriasis and/or PsA. One patient in the USK arm was identified as being pregnant on Day 77 (55 days after the week 3 administration of USK) and she subsequently withdrew from the trial and no additional follow-up information was available. After Week 12 and through to Week 26, 3 additional USK-treated subjects reported AEs leading to study agent discontinuation, with 1 report each of abdominal pain (due to prior surgery), basal cell carcinoma (recurrent), and haemorrhagic stroke. The protocol mandated discontinuation of study medication if a subject developed a malignancy or became pregnant.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal studies

In the 2 Phase III studies, markedly abnormal changes in liver function tests were infrequent but with slightly higher rates of increased serum transaminases in subjects receiving USK treatment (1.3%; 8/610) compared with placebo (0.3%; 1/305) at Week 16. At 24 weeks, the incidence of raised serum transaminases remained stable at 1.7% (12/700) for USK treated subjects – refer to Table 29. There was no relationship between abnormal liver function tests and the dose of USK. No patient treated with USK developed a significant increase in serum total bilirubin. Between Weeks 24 and 52 - 60 the incidence of abnormal liver function tests did not increase above those observed at 24 weeks. In many of the patients who developed abnormal liver function tests, there were confounding etiological factors such as obesity with fatty liver disease, concurrent hepatotoxic drugs (for example, MTX or isoniazid) and/or alcohol use.

Table 29: Number of Subjects with Markedly Abnormal Liver Function Tests Post-Baseline through to Week 24 in PSUMMIT I and PSUMMIT II Studies (Combined Dataset).

		Ustekinumab			
	Placebo	Placebo → 45 mg[a]	45 mg[b]	90 mg	Combined
Subjects treated	309	89	308	308	705
Alkaline phosphatase (elevated)					
N	305	89	307	304	700
Subjects with any abnormal value	0	0	0	0	0
Subjects with > 1 abnormal value	0	0	0	0	0
ALT (elevated)					
N	305	89	307	304	700
Subjects with any abnormal value	1 (0.3%)	0	6 (2.0%)	6 (2.0%)	12 (1.7%)
Subjects with > 1 abnormal value	0	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
AST (elevated)					
N	305	89	306	304	699
Subjects with any abnormal value	0	0	5 (1.6%)	4 (1.3%)	9 (1.3%)
Subjects with > 1 abnormal value	0	0	0	0	0
Total bilirubin (elevated)					
N	305	89	307	304	700
Subjects with any abnormal value	0	0	0	0	0
Subjects with > 1 abnormal value	0	0	0	0	0

8.4.1.2. Other studies

In Study C0743T10, 1 subject in the placebo group (before Week 12), 4 patients in the USK treatment arm (before Week 12) and 1 patient in the placebo to USK crossover group were observed to have elevations in serum AST, ALT or total bilirubin through to 36 weeks. For all of the patients, a single elevated reading of serum transaminases post-baseline was observed, which then resolved. Several of the subjects were receiving concomitant hepatotoxic drugs such as MTX, or isoniazid for TB prophylaxis in 1 case.

8.4.2. Kidney function

8.4.2.1. Pivotal studies

In both of the Phase III PsA studies, tests for kidney function did not show any treatment related mean changes from baseline over follow-up that extended to Weeks 52-60. A total of 2 patients (1 in each pivotal study) developed acute renal failure while receiving USK (45 mg or 90 mg). In both case reports there were alternative etiological explanations for the abrupt decline in renal function such as dehydration and concurrent medications such as NSAID therapy.

8.4.2.2. Other studies

No cases of significantly abnormal changes in kidney function were recorded up to 36 weeks of follow-up in Study C0743T10.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

In the 2 Phase III studies, markedly abnormal changes in other clinical chemistry (that is, excluding liver and kidney function tests) were infrequent apart from elevated non-fasting blood glucose levels, and very occasional cases of elevated serum sodium (mild and transient). However, abnormalities of both of these parameters occurred at similar rates between the USK and placebo treatment groups (4.6 - 5.7% for raised non-fasting glucose levels and 1.0% for increased serum sodium at Week 16). The incidence of both abnormalities did not increase with extended periods of follow-up in both Phase III studies (up to Weeks 52 and 60). Treatment

with USK (either dose) did not have a consistent effect compared with placebo on any lipid parameters including fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

8.4.3.2. Other studies

During the initial 12-week placebo-controlled period of Study C0743T10, markedly abnormal changes in chemistry laboratory values occurred at a low and similar incidence between the placebo and USK groups. The only markedly abnormal change occurring in more than 1 subject on more than 1 occasion in either treatment group was elevated non-fasting glucose, occurring in 2 (2.9% of 70) subjects in the placebo group and 5 (6.6% of 76) patients in the USK arm. Through to Week 36, markedly abnormal post-baseline changes in chemistry laboratory values remained infrequent. After Week 12 and through to Week 36, an additional 4 subjects reported elevated non-fasting glucose levels on more than 1 occasion, 2 in each treatment group.

8.4.4. Haematology

8.4.4.1. Pivotal studies

In the 2 Phase III studies, markedly abnormal changes in haematology laboratory values were infrequent with comparable rates between treatment groups (both doses of USK and placebo) at all applicable time points (Weeks 16, 24 and 52 - 60). Using the combined patient dataset of both Phase III PsA studies, the most frequent abnormal haematology findings in USK treated subjects were decreased absolute lymphocyte count (3.0% [21/700] at Week 24), decreased neutrophil count (1.4% [10/700] at Week 24), elevated eosinophil count (0.7% [5/700] at Week 24) and decreased haemoglobin levels (0.4% [3/700] at Week 24). There was no relationship between abnormal haematology results and dose of USK. When using only the data from the placebo-controlled period of each study, abnormal haematology findings occurred at a similar incidence and pattern in the placebo versus USK treatment groups. One patient treated with USK 45 mg developed significant thrombocytopenia between Weeks 24 and 52 in the PSUMMIT I Study. In the PSUMMIT II trial, another subject (37 year old male) developed moderate thrombocytopenia (nadir platelet count of 65 x 10^9/L) which onset on Study Day28 and persisted until last follow-up on Study Day157. The patient withdrew from USK on Study Day73, and the aetiology of the thrombocytopenia was unclear. He had been receiving concurrent MTX and abdominal ultrasonography had shown mild, non-specific hepatosplenomegaly.

8.4.4.2. Other studies

During the first 12 weeks, 1 patient treated with USK developed mild asymptomatic neutropenia. Another 3 patients developed transient mild lymphopenia (1 in the placebo arm and 2 treated with USK). No other cases of significantly abnormal changes in haematology values were recorded up to 36 weeks of follow-up in Study C0743T10.

8.4.5. Anti-drug antibodies

8.4.5.1. Pivotal studies

In both of the Phase III studies, the presence of Anti-Drug Antibodies (ADAs) in serum was determined by a validated ECLIA (Electrochemiluminescent Immunoassay) method. This newly developed assay has the advantage of being able to substantially reduce USK interference in the detection of ADAs to USK in human serum samples. The maximum observed sensitivity of the ADA ECLIA technique was 1.97 ng/mL in human serum. It was verified that the presence of USK in serum at the concentration levels studied did not interfere with the ADA ECLIA, and 50 ng/mL of ADAs to USK could be detected in the presence of up to 100 µg/mL of USK in serum. As a result, the status of ADAs to USK in the PSUMMIT studies was classified in 2 categories: positive or negative, regardless of the presence or absence of quantifiable USK concentration in serum samples.

The incidence at 24 - 36 weeks of ADAs to USK in the Phase II PsA study (C0743T10) and in the Phase III trials (PSUMMIT I and II) are summarised in Table 30. In the Phase III trials, the incidence of ADAs to USK across all dose groups through to Week 24 was 5.8% (26/448) in the PSUMMIT I Study and 6.1% (14/228) in the PSUMMIT II Study. The incidence of ADAs was slightly higher in the subjects exposed to USK 90 mg injections (6.2 - 7.1%) versus those who received USK 45 mg treatment (5.4% in both trials). At Week 24 in both Phase III studies, the incidence of ADAs was lower in those receiving concomitant MTX (3.3% in PSUMMIT I and 4.5% in PSUMMIT II) compared with subjects not taking concurrent MTX (8.1% in PSUMMIT I and 7.6% in PSUMMIT II). Furthermore, in the PSUMMIT II Study in which 57.6% (137/238) of USK exposed subjects had prior anti-TNF experience, the incidence of ADAs to USK was higher in those with a history of prior anti-TNF treatment (8.5%; n = 11) compared to those who were anti-TNF naïve (3.1%; n = 3). However this result may have been confounded by the fact that concurrent MTX use in the PSUMMIT II Study was lower in those with previous anti-TNF exposure (41.7%) compared to subjects who were anti-TNF naïve (60.6%).

Table 30: Incidence of Anti-Drug Antibodies to USK at Week 24-36 in the Phase 2 and 3 PsA Studies.

Dose Groups[a]	Subjects Treated	Subjects with Appropriate Samples[b]	Positive Status for antibodies to ustekinumab
C0743T10[c,d]			
Overall	133	124	14 (11.3%)
CNTO1275PSA3001[e,f]			
Overall	467	448	26 (5.8%)
45 mg	263	255	14 (5.4%)
90 mg	204	193	12 (6.2%)
CNTO1275PSA3002[e,f]			
Overall	238	228	14 (6.1%)
45 mg	134	129	7 (5.4%)
90 mg	104	99	7 (7.1%)

[a]Dosing in each study was multiple doses; dose groups include all subjects who received ustekinumab at any time. [b]Subjects with appropriate samples had one or more samples obtained after their first ustekinumab administration. [C]Enzyme immunoassay (EIA) was used to detect antibodies. [d]Last visit assessed for antibodies: Week 36 [e]Electrochemiluminescent immu;noassat (ECLIA) was used to detect antibodies. [f]Last visit assessed for antibodies: Week 24.

The incidence of USK-ADAs at approximately 1 year of follow-up (52 weeks in PUMMIT I and 60 weeks in PSUMMIT II) is shown in Table 31. At Week 52 in the PSUMMIT I Study the overall incidence of ADAs was 7.1% (42/591). At Week 60 in the PSUMMIT II Study the overall incidence of ADAs to USK was 9.3% (26/279). In both Phase III studies, the incidence of ADAs at Weeks 52 or 60, were similar between the combined USK 45 mg and 90 mg dose groups. Across the 2 trials, the majority of subjects (64.7%; 44/68) who were positive for ADAs had antibodies with neutralising activity for USK in vitro. In the PSUMMIT I Study, 25 of the 42 ADA (59.5%) positive subjects demonstrated neutralising activity, and in the PSUMMIT II trial, 19 of 26 (73.1%) of ADA positive patients had neutralising antibodies. Like the 24-week analysis, concurrent MTX use was associated with a lower incidence of developing ADAs (4.6% versus 10.8%), as was being anti-TNF naïve (5.6% versus 12.3%). In addition, the Week 52 - 60 analyses showed that higher subject weight (> 100 kg versus ≤ 100 kg) was associated with a higher incidence of ADAs. For those weighing > 100 kg, the incidence of ADAs was 11.5% (versus 5.6% in ≤ 100 kg) in the PSUMMIT I Study and 20.0% (versus 5.0% in ≤ 100 kg) in the PSUMMIT II Study.

Table 31: Incidence of Anti-Drug Antibodies to USK at Week 52 - 60 in the PSUMMIT Studies.

Dose Groups[a]	Subjects Treated	Subjects with Appropriate Samples[b]	Positive Status for antibodies to ustekinumab
CNTO1275PSA3001[c,d]			
All ustekinumab	598	591	42 (7.1%)
Placebo → 45 mg	189	189	11 (5.8%)
Combined 45 mg	205	203	17 (8.4%)
90 mg	204	199	14 (7.0%)
CNTO1275PSA3002[c,e]			
All ustekinumab	287	279	26 (9.3%)
Placebo → 45 mg	80	79	7 (8.9%)
Combined 45 mg	103	101	10 (9.9%)
90 mg	104	99	9 (9.1%)
Overall	885	870	68 (7.8%)

[a]Dosing in each study was multiple doses; dose groups include all subjects who received ustekinumab at any time.
[b]Subjects with appropriate samples had one or more samples obtained after their first ustekinumab administration.
[c]Electrochemiluminescent immunoassay (ECLIA) was used to detect antibodies to ustekinumab.
[d]Last visit assessed for antibodies: Week 52.
[e]Last visit assessed for antibodies: Week 60.

8.4.5.2. Other studies

In Study C0743T10 serum samples for ADAs were taken at screening, Week 12 and Week 36. In contrast to the Phase III trials, a bridging enzyme immunoassay method (EIA; older technique with less sensitivity and specificity) was used to detect ADAs to USK in serum. The maximum observed sensitivity of the EIA was 125 ng/mL in human serum and 50 ng/mL of ADAs to USK could be detected in the presence of up to 7 ng/mL (that is, 0.007 µg/mL) of USK in serum. Since the presence of USK in serum could interfere with the EIA in detecting the ADAs to USK, the antibody status was classified into 3 categories: positive, negative (no ADAs were detected and serum USK levels were unquantifiable), and detectable/inconclusive (no ADAs to USK were detected and serum USK concentrations were quantifiable). In contrast to the 2 Phase III studies, the serum samples positive for ADAs in Study C0743T10 were not further analysed for neutralising the bioactivity of USK in vitro.

Of the 133 subjects who received USK during the trial, 124 had samples evaluable for ADAs. At Week 12, no patients tested positive for ADAs. At Week 36, 11.3% (14/124) of all subjects exposed to USK tested positive for ADAs. The incidence of ADAs in this trial was higher than that recorded in the 2 Phase III studies and may reflect the difference in specificity between the 2 assay techniques used to detect ADAs. The proportion of antibody positive subjects was higher (14.0%; 7/50) in the placebo to USK crossover group compared to the original USK arm (9.5%; 7/74). In addition, the incidence of ADAs at Week 36 was lower in subjects who received MTX (2 subjects; 7.7%) compared to those who did not received concurrent MTX (12 subjects; 12.2%). Antibody titres were generally low, with 11 of the 14 anti-USK antibody positive subjects recording titres of less than or equal to 1:80. The presence of anti-USK antibodies was not associated with an increased incidence or type of AE, or diminished clinical effect (ACR and/or PASI responses).

8.4.6. Vital signs

8.4.6.1. Pivotal studies

In both of the Phase III studies, no significant treatment related changes were observed for the vital sign parameters of heart rate, blood pressure, weight and waist circumference (recorded at baseline, Week 24 and Weeks 52 - 60).

8.4.6.2. Other studies

In Study C0743T10, weight was recorded at baseline and Week 36. At Week 36, subjects in the placebo crossover group recorded a slightly higher median weight (93.8 kg) compared with baseline (92.0 kg). Among subjects in the USK treatment arm, weight at baseline and Week 36 remained relatively stable at 89.1 kg and 89.5 kg, respectively.

8.5. Post-marketing experience

USK first received marketing approval for the treatment of psoriasis in December 2008, and is currently approved in over 65 countries for this indication. At the time of submission in Australia (December 2013), no post-marketing reports anywhere in the world for the treatment indication of PsA were available as this indication was only approved in Europe and USA in September 2013. As of June 30, 2012 7 PSURs have been submitted. Hypersensitivity reactions (including rash and urticaria post-injection) and serious allergic reactions (including anaphylaxis and angioedema) have been identified from spontaneous ADR reports. The other safety concerns under surveillance are serious infection (including tuberculosis and salmonella), malignancies, major adverse cardiovascular events, neurologic disorders (including facial palsy) and pregnancy outcomes. There is also concern in the dermatology literature of a possible association between USK use in adult patients with psoriasis and the development of non-melanoma skin cancers, particularly in those > 60 years of age, with a prior history of prolonged immunosuppressant treatment or psoralen plus ultraviolet A therapy. This potential safety concern remains under surveillance.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Risk of infection, including opportunistic infection

USK has been identified to be associated with a potential increased risk of infection, including reactivation of latent tuberculosis. Screening for tuberculosis was an entry requirement of both pivotal studies in this submission. No patient in the 3 PsA trials developed reactivation of latent tuberculosis. Herpetic infections were reported at a very low frequency in both pivotal studies, with no treatment related association being apparent. The overall rate of infection related SAEs was similar in USK treated subjects versus placebo patients in both pivotal studies, but between Weeks 24 and 52 - 60, several cases of serious infection were observed in both Phase III studies.

8.6.2. Malignancies, including skin cancer

In the placebo-controlled periods of the PsA trials, the incidence of malignancies (excluding non-melanoma skin cancer) was 0.16 per 100 Patient-Years (PY) of follow-up for those who received USK (1 subject in 615 PY of follow-up) compared with 0.35 per 100 PY of follow-up in the placebo cohort (1 subject in 287 PY of follow-up). The incidence of non-melanoma skin cancer was 0.65 per 100 PY of follow-up for those who received USK (4 subjects in 615 PY of follow-up) compared with 0.70 per 100 PY of follow-up in the placebo group (2 subjects in 287 PY of follow-up). The short-term data for the risk of malignancy in patients with PsA treated with USK appears relatively benign and within expectations, however, the clinical studies thus far reported have insufficient treatment follow-up periods (ranging from 36-60 weeks) in this submission to assess the malignancy potential of USK in the target populations of PsA. Updated data from the psoriasis population experience, which is significantly larger, does not indicate an increased overall risk of malignancy (excluding non-melanoma skin cancer) when using USK, however, this issue will require ongoing surveillance in the target populations if approval is granted.

8.6.3. Injection site and hypersensitivity reactions

This has already been addressed in this report. ISRs are uncommon, mild in severity and have not been associated with premature discontinuation of study medication. Furthermore, no major hypersensitivity reactions have been observed.

8.6.4. Cardiovascular safety

Patients with PsA are known to be at an increased risk of occlusive atherosclerotic vascular disease such as myocardial infarction and stroke. A total of 4 major adverse cardiovascular events have been recorded in the PsA trials included in this submission. All 4 events did not result in death, and 2 of the cases were myocardial infarction (1 in a placebo treated subject and the other in a patient given USK 45 mg injections) and the other 2 reports related to stroke (USK 45 mg and USK 90 mg). The rate of major cardiovascular adverse event is low (0.55 - 0.78 per 100 PY) and within expectations for the target population.

8.6.5. Unwanted immunological events

The rate and consequences of developing anti-USK antibodies has already been discussed in this report. The formation of ADAs does not appear to be associated with experiencing AEs, but results in increased plasma clearance of the drug, which potentially may affect efficacy.

In this submission, no subjects developed clinical consequences consistent with systemic autoimmune disease (such as systemic lupus erythematosus) or major neurologic disorders. However, 1 subject (in the placebo to USK 45 mg crossover group) in Study C0743T10 developed rebound of psoriasis within 3 months of receiving their last dose of USK.

8.7. Other safety issues

8.7.1. Safety in special populations

In the PsA studies to date, 3 subject pregnancies and 2 partner pregnancies have been reported. No further information on the outcome of each of these pregnancies has been provided.

No formal study of drug-drug interaction has been performed with USK, and there is no data on the effect of USK upon vaccine responses in the PsA population.

During the 3 PsA studies, there was no safety signal to indicate that the concomitant use of MTX or past exposure to anti-TNF therapy was associated with an increased incidence or type of AE. However, obesity (that is, subject weight > 100 kg) does appear to confer an increased risk of AEs, particularly for infection related AEs. This observation is not unexpected, as it has been observed for various drugs including MTX and other biologic DMARDs.

8.8. Evaluator's overall conclusions on clinical safety

In this submission, the total clinical safety dataset for the use of USK in adult patients with active PsA consists of 914 patients involved in 2 pivotal Phase III studies (PSUMMIT I and II) and 1 supporting Phase II trial (C0743T10), 692 (75.7%) of whom received USK for at least 6 months and 213 (23.3%) subjects were exposed to USK for at least 1 year. USK therapy was given by SC injection either at a dose of 45 mg, 63 mg or 90 mg. Both of the proposed doses in PsA (45 mg and 90 mg) had more than 300 subjects exposed to USK for at least 6 months. Approximately half of the patients in the dataset received concurrent MTX, more than 75% were taking concomitant NSAID, and approximately one sixth were taking concurrent low dose oral CS. In the PSUMMIT II trial, more than half of all subjects had received prior biologic therapy, mainly with anti-TNF therapy. Overall, there is a sufficient volume of data to make a meaningful assessment of USK safety for up to 52 weeks of treatment in the newly proposed treatment indication of active PsA.

Infection was the most common AE recognised in the PsA studies, and these appeared to occur at a slightly higher frequency in the USK treatment groups versus control during the placebo controlled treatment periods (12 - 16 weeks). The majority of infections were mild in severity, self-limiting, and were predominately either nasopharyngitis or URTI. Some gastrointestinal AEs were also more common in USK treated subjects, particularly diarrhoea and nausea. The use of concurrent MTX or prior exposure to anti-TNF therapies did not appear to increase the overall risk of AEs, including infection related AEs. However, subject weighing > 100 kg had a higher incidence of overall and infection related AEs. SAEs including serious infection related events were reported in a low proportion of USK-treated patients in both pivotal trials (< 3%). No patients developed reactivation of latent tuberculosis, and no other significant opportunistic infections were observed.

Injection site reactions were an uncommon type of AE reported in patients receiving USK (1.5 - 2.5% incidence in the Phase III studies). The majority of injection site reactions were mild, resolved without specific intervention and did not result in discontinuation from USK therapy. No acute systemic hypersensitivity reactions were reported with USK in the 3 PsA trials, and only 1 case of rebound psoriasis was reported in a USK treated subject in the 2 pivotal studies. Discontinuations due to AEs occurred at a low and similar frequency in USK versus placebo treated subjects.

No deaths were reported in the 3 PsA studies. Regarding major adverse cardiovascular events, a total of 8 events were recorded in USK treated subjects in the extended follow-up periods (ranging from 36 - 60 weeks) of the 3 PsA studies. These AEs included 5 myocardial infarcts, 2 cases of cerebrovascular accident (including 1 case of cerebral haemorrhage) and there was 1 report of atrial fibrillation. All of the patients had significant risk factor profiles for suffering major adverse cardiovascular events, and the relationship between these types of AEs and USK remains unclear. Three patients developed malignancies in the PsA studies (2 reports in PSUMMIT II and 1 case in Study C0743T10). Two of the cases related to non-melanoma skin cancer and the other patient suffered breast cancer. Overall, longer periods of treatment follow-up are required to inform about this potential safety signal.

No significant abnormalities of laboratory values (such as elevations in hepatic transaminases) compared with placebo have been associated with USK in the PsA study program. Some patients developed increases in non-fasting blood glucose and liver function tests which were mild and without associated clinical sequelae. There were couple of cases of significant thrombocytopenia observed in patients treated with USK and mild-moderate asymptomatic lymphopenia has also been observed.

The incidence of PsA subjects developing anti-USK antibodies is approximately 7.1 - 9.3% at 52 - 60 weeks using the combined USK treated datasets in the PSUMMIT studies, and their clinical relevance for safety outcomes is yet to be defined with no discernible link to the risk of infection, or injection related reactions. However, the development of anti-USK antibodies may be associated with a lack or loss of efficacy.

In summary, the safety data indicates that USK has an acceptable overall safety profile up to 52 weeks of therapy in the treatment of adult patients with moderately to severely active PsA. There is limited long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and adverse cardiovascular events, which will require longitudinal safety follow-up. There are some significant identified safety concerns including the risk of serious infection, opportunistic infection, injection related hypersensitivity and allergic reactions, and neurologic disorders. These safety concerns are consistent with the known profile of USK in the approved indication of psoriasis. Significant pharmacovigilance would be required if approval is granted for extension of treatment indications. This would include vigilance for opportunistic infections, adverse cardiovascular events and malignancy (particularly, non-melanoma skin cancers).

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of USK in the proposed usage are:

- Clinically meaningful improvements in the clinical signs and symptoms of PsA (that is, ACR response criteria), as well as physical functioning and QOL indices when given to patients with active PsA who have failed to respond to conventional treatment (DMARD [mainly MTX] and NSAID).
- In addition to the joint disease of PsA, USK is an effective therapy for associated soft tissue manifestations such as enthesitis and dactylitis, as well as co-morbidities such as skin psoriasis and spinal disease symptoms.
- Provides an alternative biologic therapy (different mechanism of action) to anti-TNF drugs in patients with active PsA who have failed to respond to conventional treatment.
- Convenient dosing schedule (every 12 weeks in the maintenance phase of therapy) using a convenient mode of administration (SC injection via prefilled syringe).

9.2. First round assessment of risks

The risks of USK in the proposed usage are:

- Increased incidence of minor infection (particularly nasopharyngitis and URTI) compared with placebo, as well as other mild AEs such as diarrhoea, nausea and headache.
- Potential for serious infection including reactivation of latent tuberculosis and other serious opportunistic infections.
- Local injection site reactions, which are generally mild and transient, and do not result in permanent discontinuation from USK.
- Potential increased risk of malignancy (particularly, non-melanoma skin cancers) and adverse cardiovascular events requiring long-term surveillance.
- Formation of anti-USK antibodies which results in increased plasma clearance of USK and possible loss, or lack of efficacy.
- Slower onset of action than anti-TNF drugs in treating the symptoms and signs of active PsA, but similar response rates at 52 weeks of treatment follow-up (indirect data comparison).
- Patients weighing > 100 kg require a larger dose (90 mg) compared to those weighing ≤ 100 kg (45 mg).

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of USK for up to 60 weeks of treatment follow-up in the target population of adult subjects with active PsA is favourable.

10. First round recommendation regarding authorisation

The evaluator recommends the acceptance of the sponsor's proposed extension of treatment indications for USK to include the treatment of active PsA. Approximately half of all subjects in the 3 PsA studies took MTX concurrently with USK, and the beneficial clinical responses in those not taking concomitant MTX were similar. Hence the sponsor has justified the claim of using

USK in patients with PsA with or without MTX. Furthermore, the studies recruited subjects with active PsA who had failed to adequately respond to conventional treatment (DMARD [mainly MTX] and/or NSAID), but did include a subset of patients with prior biologic therapy exposure (mainly, anti-TNF medicines). The evaluator recommends the Australia proposed treatment indication include a short phrase consistent with the EU wording indicating that USK be used as a second line therapy following the failure of conventional DMARD and/or NSAID.

The proposed wording of treatment extension in patients with PsA has an additional element relating to inhibition of structural progression of peripheral joint damage by X-ray. The current submission provides robust evidence of improving the symptoms and signs of active PsA, as well as physical functioning. However, the radiographic claim has not been sufficiently proven at this stage, and requires further evidence of justification before registration is approved. In particular, the current X-ray data is limited to 52 weeks of assessment which is an insufficient time frame to evaluate such a claim. Furthermore, the current X-ray data only shows a positive effect with USK in 1 of the 2 pivotal studies (PSUMMIT II did not show a treatment related effect with USK versus placebo at 24 weeks) and in subjects without prior anti-TNF exposure. This observation may have occurred because of the data handling rules and associated imputation factors, but nonetheless no consistent treatment related radiographic effect with USK could be demonstrated in the current dataset. It would be important to review the 2 year radiographic data from the PSUMMIT I Study to determine if a robust treatment effect with USK could be observed.

Consistent with the submitted data as well as the approved EU treatment indication wording, the evaluator recommends the following indication wording '*Stelara, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients when the response to previous non-biological DMARD therapy has been inadequate*.'

Should approval of the sponsor's proposed extension of indication be granted, the evaluator also recommends that approval of the sponsor's proposed extension of indication be subject to:-

- Satisfactory response to the questions in section 12 of this report,
- Regular periodic safety update reports, and
- When available, the sponsor provides the TGA with the final clinical study report for the PSUMMIT I Study (that is, at 108 weeks of treatment follow-up).

11. Clinical questions

11.1. Pharmacokinetics

1. No formal drug-drug interaction studies with Stelara have been performed. Cytokines have the potential to alter the expression of cytochrome P450 enzymes. Could the sponsor comment on whether Stelara has the potential for drug-drug interactions on the basis of an alteration in cytokine levels and/or activity.

11.2. Pharmacodynamics

2. Has the sponsor evaluated the potential for polymorphisms in the IL-23/Th-17 and IL-12/Th-1 pathways as having an impact upon the effect of Stelara?

11.3. Efficacy

3. In the current approved Product Information, dose adjustment (that is, reducing the dose interval from 12 to 8 weeks) is possible for patients with psoriasis demonstrating inadequate response. Could the sponsor confirm that no such dose adjustment strategy is being requested for the psoriatic arthritis treatment indication?
4. The claim of radiographic benefit with Stelara in patients with active psoriatic arthritis is primarily based on a treatment related effect observed in the PSUMMIT I Study (but not demonstrated in the PSUMMIT II trial) on assessments performed after 24 weeks of treatment. Moreover, for subjects weighing > 100 kg, no treatment effect was seen in patients receiving Stelara when compared to placebo treated subjects. Could the sponsor comment on the robustness of the claim of inhibiting structural progression given the limitations of the current dataset (that is, treatment effect has not been consistently demonstrated in both pivotal studies and across all patient subgroups).
5. Another limitation of the current X-ray dataset is the duration of treatment follow-up. Although there is no specific regulatory advice on the minimum required time intervals for evaluating X-ray outcomes in psoriatic arthritis, regulatory guidelines in RA recommend a longer period of follow-up (beyond 12 months) before a radiographic claim can be made. Could the sponsor comment on whether the 2 year radiographic data from the PSUMMIT I Study should be considered before a robust treatment effect with Stelara on radiographic outcomes be assessed?

11.4. Safety

6. Has the sponsor performed any vaccine sub-studies in patients with psoriatic arthritis to determine the effect of Stelara on protective immune status?

12. Second round evaluation of clinical data submitted in response to questions

The sponsor has responded to 6 clinical questions that were raised in the first round clinical assessment (response dated 25 August 2014). Each of these responses will be assessed in order.

12.1. Pharmacokinetics

12.1.1. Question 1

No formal drug-drug interaction studies with Stelara have been performed. Cytokines have the potential to alter the expression of cytochrome P450 enzymes. Could the sponsor comment on whether Stelara has the potential for drug-drug interactions on the basis of an alteration in cytokine levels and/or activity.

12.1.1.1. Sponsor's response:

Although no formal drug interaction studies have been performed, the sponsor reports that it has conducted in vitro studies that indicate that IL-12 and IL-23 do not modulate the expression of the major CYP enzymes, indicating that no dose adjustments are required in patients receiving concomitant CYP450 metabolised drugs with USK. In addition, the US FDA agreed that *in vivo* drug interaction studies for USK were not required.

12.1.1.2. Evaluators comment:

The sponsor response is acceptable with no further action.

12.2. Pharmacodynamics

12.2.1. Question 2

Has the sponsor evaluated the potential for polymorphisms in the IL-23/Th-17 and IL-12/Th-1 pathways as having an impact upon the effect of Stelara?

12.2.1.1. Evaluators comment on the sponsor's response:

The sponsor states that no single nucleotide polymorphisms in the T-helper cell pathway (Th-1 or Th-17) relating to the effect of USK have been identified using immunochip analysis of the PsA data. Hence, it is unlikely that polymorphisms in these immune pathways may influence the effect of USK, which is an acceptable assumption.

12.3. Efficacy

12.3.1. Question 3

In the current approved product information, dose adjustment (that is, reducing the dose interval from 12 to 8 weeks) is possible for patients with psoriasis demonstrating inadequate response. Could the sponsor confirm that no such dose adjustment strategy is being requested for the psoriatic arthritis treatment indication?

12.3.1.1. Evaluators comment on the sponsor's response:

The sponsor confirms that no dose adjustment for inadequate responders was studied in the PsA clinical studies, and therefore a dose adjustment strategy is not being requested for the PsA treatment indication. The dosing discrepancy between the 2 treatment indications (psoriasis and PsA) has the potential to result in off label use for Stelara in the PsA indication, although the proposed PI is clear about the differences in dosing across the 2 treatment indications.

12.3.2. Question 4

The claim of radiographic benefit with Stelara in patients with active psoriatic arthritis is primarily based on a treatment related effect observed in the PSUMMIT I Study (but not demonstrated in the PSUMMIT II trial) on assessments performed after 24 weeks of treatment. Moreover, for subjects weighing > 100 kg, no treatment effect was seen in patients receiving Stelara when compared to placebo treated subjects. Could the sponsor comment on the robustness of the claim of inhibiting structural progression given the limitations of the current dataset (that is, treatment effect has not been consistently demonstrated in both pivotal studies and across all patient subgroups).

12.3.2.1. Evaluators comment on the sponsor's response:

The sponsor concurs with the above statement that the beneficial effect of USK on limiting structural damage progression was only observed in the PSUMMIT I Study and for those subjects weighing ≤ 100 kg. As per the original submission, the sponsor provides several possible explanations for the inconsistency of the X-ray results between the PSUMMIT I and PSUMMIT II studies including a higher rate and non-random pattern of missing data observed in the PSUMMIT II Study (versus PSUMMIT I), a smaller heterogeneous population of anti-TNF experienced and naïve patients in the PSUMMIT II Study (versus subjects being TNF naïve in PSUMMIT I) as well as the anti-TNF naïve subpopulation (42% of all subjects) in the PSUMMIT II Study showing lower inflammatory disease activity at baseline (versus PSUMMIT I). All 3 of the above hypotheses are valid explanations for the inconsistent X-Ray results across the 2 pivotal PsA trials. In the S31 response, the sponsor has included a post-hoc analysis from the anti-TNF naïve subgroup of the PSUMMIT II Study showing that that those with a higher inflammatory activity at baseline (defined as CRP ≥ 10 mg/L) had less X-ray progression at 24 weeks (defined as change from baseline in the total modified vdH-S score) when treated with USK (n = 39 for the combined USK group) versus control therapy (n = 14 subjects), particularly

at the 90 mg dose (n = 20 subjects). Published literature supports the proposal that elevated CRP values are a risk factor for X-ray progression in PsA (Gladman et al, 2010). However, a significant limitation of the post-hoc, subgroup analyses was that only small patient groups were available to be investigated which makes the results susceptible to invalidity. In addition, in the anti-TNF naïve subgroup of the PSUMMIT II Study with CRP < 10 mg/L at baseline, no treatment effect with USK (n = 51 for the combined USK group) versus placebo (n = 28) was observed. Furthermore, in the anti-TNF experienced subjects of the PSUMMIT II Study, no treatment effect with USK (n = 118 for the combined USK group) over control (n = 62) was observed, regardless of baseline CRP reading.

In support of the consistency of the findings, the sponsor has also submitted 2 additional post-hoc analyses based on modelling of the X-ray progression using the results of the 2 anti-TNF naïve populations from the PSUMMIT studies. In these analyses, a logistic regression model based on the PSUMMIT I Study X-ray data was developed using observed data, which was then applied to the anti-TNF naïve subgroup of the PSUMMIT II trial to calculate the predicted progression status. The model showed that the anti-TNF naïve subgroup of the PSUMMIT II Study recorded observed X-ray data (that is, for the change from baseline to Week 24 in total modified vdH-S score) within the predicted cut-offs for progression (tested by a 1-sample t-test), suggesting this patient subgroup was similar between the 2 pivotal trials.

Regarding inhibition of structural damage in subjects weighing > 100 kg, the sponsor has included post-hoc analyses examining X-ray progression by subject weight (≤ 100 kg versus > 100 kg) within each of the PSUMMIT studies. In the PSUMMIT 1 Study, a treatment effect with USK was observed in both weight strata, though the treatment effect was greater in subjects weighing ≤ 100 kg but the difference in treatment effect in this subgroup was primarily driven by a larger placebo progression for subjects weighing ≤ 100 kg (mean change of 1.44 [n = 154] in the placebo group versus 0.21 in the combined USK group [n = 307]). In the PUSUMMIT I Study, the mean change from baseline to Week 24 in the modified vdH-S score was 0.50 in the placebo treated patients weighing > 100 kg (n = 52) versus 0.26 in the combined USK treatment group weighing > 100 kg (n = 102). In the PSUMMIT 2 Study, inhibition of radiographic progression was observed in USK treated subjects weighing ≤ 100 kg (mean change from baseline of 0.48 [n = 147] versus 0.73 in the matched placebo treated cohort [n = 74]) mg group, though the magnitude of USK treatment effect was lower than that observed in the PSUMMIT 1 Study. However, in the PSUMMIT II Study, no USK treatment effect was observed in subjects weighing > 100 kg (mean change from baseline of 1.37 in the combined USK group [n = 60] versus - 0.02 in the matched placebo treated group [n = 30]).

In summary, the totality of the X-ray data does not demonstrate a consistent robust effect with USK that supports the claim of inhibiting structural progression. The current dataset has not shown a consistent treatment effect with USK in both pivotal PsA studies and across all patient subgroups.

12.3.3. Question 5:

Another limitation of the current X-ray dataset is the duration of treatment follow-up. Although there is no specific regulatory advice on the minimum required time intervals for evaluating X-ray outcomes in psoriatic arthritis, regulatory guidelines in RA recommend a longer period of follow-up (beyond 12 months) before a radiographic claim can be made. Could the sponsor comment on whether the 2 year radiographic data from the PSUMMIT I Study should be considered before a robust treatment effect with Stelara on radiographic outcomes be assessed?

12.3.3.1. Evaluators comment on the sponsor's response:

In the response, the sponsor has provided the week 100 radiographic results for the PSUMMIT I Study to support the claim of X-ray benefit with USK in PsA. The week 100 data appropriately focussed on the maintenance of radiographic benefit by evaluating whether the mean changes in the modified total vdH-S score from baseline remained constant or increased over time. The

data beyond the 24 week placebo-controlled period is limited by the lack of a control arm as many patients initially randomised to placebo were switched to USK at or before 24 weeks of follow-up.

Between Weeks 52 and 100, subjects who were initially randomised to USK 45 mg (n = 205) had a mean change in total modified vdH-S scores of 0.48 (compared with the mean change from baseline to Week 52 of 0.48), and for the USK 90 mg group (n = 204) the mean change between Week 52 and 100 was 0.63 (compared to 0.55 for baseline to Week 52). This data indicates that mean changes for both USK treatment groups between the 2 follow-up periods was similar, which is consistent with maintenance of treatment effect. Patients initially randomised to placebo that began receiving USK 45 mg injections at either Week 16 or 24 (n - 185 subjects) had a mean change in the total modified vdH-S score of 0.77 between Weeks 52 and 100 compared with a mean change of 1.49 between baseline and Week 52. These results indicate that the rate of radiographic progression between Weeks 52 and 100 decreased with the commencement of USK in those originally administered placebo in the PSUMMIT I Study.

The response also included data showing the cumulative change in the modified vdH-S score from baseline to Week 52, as well as the change from baseline to Week 100 – refer to Table 32. Across all 3 treatment cohorts, the median change from baseline to Week 100 in the total modified vdH-S score was 0. However, the cumulative mean changes from baseline through to Week 100 in all 3 treatment groups increased to suggest accrued X-ray damage over time, albeit at a slower rate in those treated with either dose of USK.

Table 32: Cumulative Change from Baseline to Week 52 and 100 in total Modified van der Heijde Score in PSUMMIT I Study.

		Ustekinumab		
	Placebo → 45 mg [a]	45 mg	90 mg	Combined
Subjects randomized	189	205	204	409
Week 52				
Change from baseline				
N	189	205	204	409
Mean (SD)	1.49 (8.182)	0.48 (2.471)	0.55 (2.965)	0.51 (2.726)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Range	(-4.5; 104.5)	(-10.5; 12.4)	(-15.5; 17.5)	(-15.5; 17.5)
Week 100				
Change from baseline				
N	189	205	204	409
Mean (SD)	2.26 (12.578)	0.95 (3.816)	1.18 (5.052)	1.07 (4.471)
Median	0.00	0.00	0.00	0.00
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Range	(-4.2; 161.0)	(-11.0; 31.0)	(-18.0; 41.0)	(-18.0; 41.0)

[a] Subjects who did not receive ustekinumab are excluded.

12.4. Safety

12.4.1. Question 6:

Has the sponsor performed any vaccine sub-studies in patients with psoriatic arthritis to determine the effect of Stelara on protective immune status?

12.4.1.1. Evaluators comment on the sponsor's response:

The sponsor has not performed any vaccine sub-studies in patients with PsA, however, immune responses (that is, antibody titres) to vaccination with tetanus and pneumococcus during the long-term extension of a Phase III study (C0743T09) in PSOR showed similar responses among USK and control treated subjects. It is reasonable for the sponsor to conclude that patients with PsA are anticipated to demonstrate a similar vaccination response to those with PSOR when treated with USK, and therefore no specific safety concerns related to this issue are expected.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to the clinical questions regarding efficacy, the benefits of USK in the proposed usage are unchanged from those identified in the first round assessment of benefits.

13.2. Second round assessment of risks

After consideration of the responses in the sponsor's response, the risks of USK in the proposed usage are unchanged from those identified in the first round assessment of risks..

13.3. Second round assessment of benefit-risk balance

Overall, the benefit-risk balance of USK in the treatment of adult subjects with active PsA is favourable when introduced after a failure to or intolerance of conventional DMARD and/or NSAID therapy.

14. Second round recommendation regarding authorisation

The evaluator recommends the acceptance of the sponsor's proposed extension of registration for USK to include the treatment indication of active PsA. However, the evaluator does not recommend acceptance of 2 additional elements to the sponsor proposed indication wording. Firstly, the evaluator recommends that the Australia proposed treatment indication include a specific phrase consistent with the EU wording indicating that USK be used as a second line therapy following the failure of conventional DMARD and/or NSAID. The sponsor disagrees with this proposal. However, the pivotal PSUMMIT studies predominately recruited subjects with active PsA who had failed to adequately respond to conventional treatment (DMARD [mainly MTX] and/or NSAID). Approximately 80% of all subjects in the PSUMMIT I Study and about 86% of patients in the PSUMMIT II trial had been previously exposed to DMARDs. In addition, almost 90% of subjects in the PSUMMIT I Study had a past history of taking NSAIDs and approximately 85% of patients in the PSUMMIT II trial had this same history of prior medication use. Overall, the subgroup of enrolled patients in the pivotal Phase PsA trials without previous exposure to DMARDs and/or NSAIDs is too small to make a robust claim of USK being used as a first line therapy in active PsA.

Secondly, the totality of the current X-ray dataset does not robustly support the sponsor claim of inhibition of structural progression as assessed by peripheral joint damage on plain X-ray. In particular, a beneficial radiographic effect with USK has not been consistently demonstrated in both pivotal studies and across all patient subgroups (that is, no significant treatment effect in those with previous TNF exposure and/or weighing > 100 kg, particularly if CRP values are < 10 mg/L).

15. References

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