15 September 2016
EMA/87810/2017 Corr.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stelara

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/000958/X/0049/G

Note

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

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Table of contents

List of abbreviations

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADR	adverse drug reaction
AE	adverse event
AZA	azathioprine
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CRP	C-reactive protein
CSR	clinical study report
ECLIA	electrochemiluminescent immunoassay
EMA	European Medicines Evaluation Agency
FDA	Food and Drug Administration (US)
HSTCL	hepatosplenic T-cell lymphoma
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IFN-γ	interferon-gamma
IL	interleukin
IMCA	Icelandic Medicines Control Agency
IV	intravenous
LIV	liquid in vial
LOR	loss of response
LTE	long-term extension
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MCS	Mental Component Summary
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MPA	Medical Products Agency (Sweden)
MTX	methotrexate
NMSC	nonmelanoma skin cancer
OR	odds ratio
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)
PsA	psoriatic arthritis
q8w	every 8 weeks
q12w	every 12 weeks
RMP	Risk Management Plan
RPLS	reversible posterior leukoencephalopathy
SAE	serious adverse event
SES-CD	Simplified Endoscopic Activity Score for Crohn's Disease
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SF-36	36-item Short Form Health Survey
SIR	standardized incidence ratio
SmPC	Summary of Product Characteristics
TB	tuberculosis
Th1	T-helper cell 1
Th17	T-helper cell 17
TNF	tumor necrosis factor

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder, Janssen-Cilag International N.V. (MAH) submitted to the European Medicines Agency (EMA) on 27 November 2015, an application for a grouping of variations in accordance with Article 7(2) of Commission Regulation (EC) No 1243/208, consisting of an extension of the marketing authorisation and a type II C.1.6.a variation.

The MAH applied for an extension of the marketing authorisation consisting of a new route of administration, additional pharmaceutical form and a new strength 130 mg concentrate for solution for infusion intravenously.

The applicant applied for the following indication:

STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, were intolerant to conventional therapy or a TNFα antagonist or have medical contraindications to such therapies

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2 c, d and e) thereof – Extension of marketing authorisation

Article 16 of Commission Regulation (EC) No 1234/2008 – "Prior Approval" procedure for major variation of type II

Article 7(2) of Commission Regulation (EC) No 1234/2008- Grouping of variations

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on MAH's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0045/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0045/2014 was not yet completed as some measures were deferred.

Additional data/marketing protection

The MAH requested consideration of one additional year of marketing protection in regard of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Greg Markey Co-Rapporteur: David Lyons

- The application was received by the EMA on 27 November 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 March 2016.
- During the meeting on 14 April 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 14 April 2016.
- During the meeting on 24 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 April 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 June 2016.
- During the PRAC meeting on 7 July 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 7 July 2016.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 31 August 2016.
- During the meeting on 15 September 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Stelara on 15 September 2016.
- The CHMP adopted a report on the significant clinical benefit for Stelara in comparison with existing therapies on 15 September 2016.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Crohn's disease is a chronic inflammatory disorder that can affect any part of the gastrointestinal tract. Patients present with persistent diarrhoea, abdominal pain and weight loss.

2.1.2. Epidemiology

The incidence in Europe is about 10 per 100,000. It is understood that the incidence and prevalence are rising worldwide.
Crohn's disease may present at any age though it more commonly presents in young adults. Both sexes are affected equally. It is more common in the presence of a family history in first degree relatives.

2.1.3. Biologic features

There are many theories of the underlying pathophysiology of Crohn's disease. In one such theory, intestinal antigen-presenting cells in Crohn's disease secrete IL-12 and IL-23. IL-12 induces immune cells toward a T helper 1 (Th1) phenotype (stimulates interferon-gamma [IFN-γ] production) while IL-23 induces a T helper 17 (Th17) pathway (promotes secretion of IL-17A, IL-21, and IL-22). Both cytokines stimulate TNF production, resulting in the intestinal inflammation and epithelial cell injury typical of Crohn's disease.

2.1.4. Clinical presentation and diagnosis

Any part of the gastrointestinal tract may be affected from the mouth to the anus, with the ileum, colon and perineum most frequently involved. Affected tissue is identified by well-demarcated areas of thickened bowel, stenosis, adhesions, local lympho-adenopathy and fistulae. Typical endoscopic features include isolated aphthous ulcers, deep ulceration, a cobblestone appearance of the gut lining and polyp formation.
Histologically, Crohn's disease is characterised by trans-mural inflammation of the intestine. Inflammation may be non-specific or may be present as focal or diffuse granulomata. Extra-intestinal manifestations may affect the skin, joints, liver, biliary tree and eyes.
Diagnosis is achieved by a combination of clinical, laboratory, radiological, endoscopic and histological findings. Management of patients is usually done within secondary care settings. The natural history of patients is to undergo repeated hospital admissions and multiple operations and to be susceptible to under-nutrition and malignancy. Crohn's disease is a chronic condition that relapses and remits. It has a global impact on patients' education, work, social and family life.
Despite the availability of many chemical and immunological treatments for Crohn's disease there remains a sub-set of patients who are unresponsive to and/or intolerant of treatments with already

authorised drugs. Because the condition is often persistent over decades, is debilitating and is often a major impediment to patients' quality of life there is a need for additional treatment options.

2.1.5. Management

About the product

Stelara (ustekinumab, CNTO 1275) is a fully human immunoglobulin G1 kappa monoclonal antibody that binds with high affinity and specificity to the p40 subunit common to both human IL-12 and human IL-23 and so neutralises their biological activities. Stelara may have a role in the management of Crohn's disease because IL-12 and IL-23 are involved in the pathophysiology of Crohn's disease.
Stelara (ustekinumab, EMEA/H/C/0958) was first authorised in the EU in January 2009 for the indication of plaque psoriasis. An extension to the indication was granted in 2013 to add psoriatic arthritis and a further extension to the indication was granted in 2015 to add the indication for paediatric plaque psoriasis in subjects aged 12yrs and older. The company now claims the indication for Crohn's disease.
The company has developed an intravenous formulation of Stelara specifically for the indication of Crohn's disease and to accompany the subcutaneous formulation already licensed.

The indication claimed is:
"STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, were intolerant to conventional therapy or a TNFα antagonist or have medical contraindications to such therapies."

Only editorial changes were done to the indication during this procedure.

The approved indication is:
"STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response *with*, lost response *to*, *or* were intolerant to *either* conventional therapy or a TNFα antagonist or have medical contraindications to such therapies."

With regards to posology it is claimed to administer the product in Crohn's disease first as a single intravenous dose which is followed up by subcutaneous administrations every 8 weeks. Dosing every 12 weeks after the first subcutaneous dose may be acceptable for patients with a lower inflammatory burden. Patients who inadequately respond to 90 mg subcutaneous dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks.
Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit by Week 16.

Type of Application and aspects on development

The Marketing Authorisation Holder (MAH) for Stelara (ustekinumab) seeks an extension to the therapeutic indication to add the treatment of adult patients with moderately to severely active Crohn's

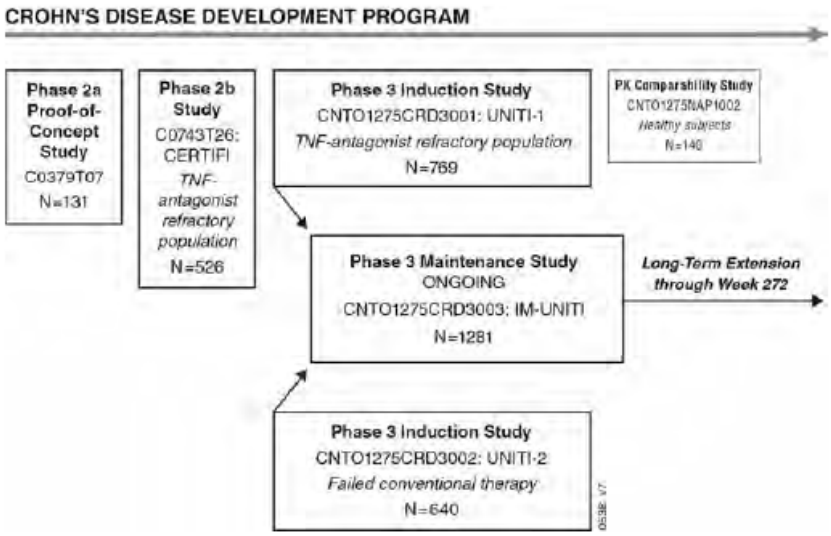
disease who have failed on or been intolerant of anti-TNF therapy; the application also introduces a new dosing regimen, a new strength of the product, and a new pharmaceutical form.

The clinical development programme for ustekinumab in Crohn's disease consists of:

- one phase I study
- two placebo-controlled phase II studies
- three placebo-controlled phase III studies

Studies are depicted in the following diagram:

Figure 1: Development program for ustekinumab in Crohn's disease



The company did not seek EMA scientific advice. Relevant CHMP guidance documents are:

Guideline on the development of new medicinal products for the treatment of Crohn's disease, CPMP/EWP/2284/99 Rev. 1, July 2008.

Points to consider on clinical investigation of medicinal products for the management of Crohn's disease, CPMP/EWP/2284/99, Jun 2001.

The chosen primary end-point of the pivotal trials did not fully comply with current CHMP guidance regarding duration of study. However, acknowledging that the clinical development of Stelara in the indication of Crohn's disease was initiated before the final version of the current guideline was published the development program can be considered overall compliant with the relevant CHMP guidelines.

2.2. Quality aspects

2.2.1 Introduction

Stelara (ustekinumab, CNTO 1275) is a fully human immunoglobulin G1 kappa monoclonal antibody that binds with high affinity and specificity to the p40 subunit common to both human IL-12 and human IL-23 and so neutralises their biological activities.

The Applicant has developed an intravenous (IV) formulation of Stelara – concentrate for solution for infusion, 130 mg - specifically for the indication of Crohn's disease and to accompany the subcutaneous formulation already licensed. It is intended that in the indication of Crohn's disease.

2.2.2 Active Substance

This line extension application did not introduce any change to the active substance.

2.2.3 Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is composed of 5 mg/mL ustekinumab formulated with a histidine buffer, sucrose, EDTA disodium salt dihydrate, L-methionine, polysorbate 80 and water for injections at pH 6.

The ustekinumab final vialed product for IV administration is supplied as a single-use, sterile solution designed to deliver 130 mg of ustekinumab in a 30 mL, Type-1 glass vial. The vials are stoppered with coated stoppers and sealed with aluminium flip-off seals. The vials are filled to deliver no less than 26 mL, the nominal deliverable volume for a 130 mg dose.

Dilution with 0.9% weight/volume sodium chloride should be performed before administration. If necessary, the diluted infusion solution may be stored up to 4 hours at room temperature.

Satisfactory background information was provided for active substance, excipients, formulation development and physiochemical and biological properties.

The description of excipients is supplemented with risk assessments regarding the use of EDTA and methionine in the formulation. Both substances have been used as excipients in other products, and it seems that they pose no significant risk in this context.

The Applicant has set out the principles of the product development studies. The level of polysorbate 80 was increased in the present formulation to protect the active substance. The studies presented are sufficient to demonstrate the protective effect of polysorbate 80 at the concentration chosen. A small contribution of polysorbate 80 to the aggregate peak in analysis with Dual wavelength - Size Exclusion – High Performance Liquid Chromatography (DW-SE-HPLC) is seen, which has been described in the literature and is accepted. Stability studies further underline the protective effect of polysorbate 80.

During the development of the control strategy for the finished product, the Applicant has employed elements of the enhanced approach. Based on the quality target product profile (QTPP) the Applicant has assessed key quality attributes for criticality in an iterative process and devised a list of critical quality attributes (CQAs), critical process parameters (CPPs) and in-process control (IPCs).

In relation to IPCs the Applicant has submitted information from various stages of validation with the aim of providing a justification for the IPC acceptance criteria and additionally provided the validation of the parameters to be used for the bubble point filter integrity test. This is accepted.

The rationale behind choosing the container closure system and its development is adequately described. As part of the compatibility studies, the Applicant conducted a standard leachable and extractables study. A dye-ingress study was conducted to support the container integrity, both after closure and after shipment.

The compatibility of the finished product with the infusion solution and polymeric containers and tubing was sufficiently shown. The data show that the infusion solution is stable for the requested 4 hour in-use time.

Manufacture of the product and process controls

Ustekinumab final vialed product for infusion is manufactured with ustekinumab active substance (target 90 mg/mL).

The manufacturing process consists of shipping, receipt, and storage of the active substance. This is followed by thawing of the active substance, pooling and mixing, pre-filtration of the pooled and mixed active substance, dilution of the active substance with pre-filtered formulation buffer and mixing to produce a homogeneous solution, pre-filtration of the solution, sterile filtration, and aseptic filling into vials (30 mL vial). Following aseptic filling, the vials are stoppered and capped. The vials are then optically inspected and stored at 2-8 °C until ready for labelling and secondary packaging. After labelling and secondary packaging, the vials are then stored at 2-8 °C prior to shipment.

The Applicant has set out the manufacturers and batch formula sufficiently. The manufacturing process is described with sufficient detail and the process parameters are provided in a separate table, including proven acceptable ranges. IPCs are also listed. Where appropriate, information on the analytical methods and their validation is provided for the IPCs.

Overall sufficient information is provided on the process validation runs.

The Applicant has given a very detailed description of the overall statistical approach and enhanced sampling plan used in the process validation. The employed acceptable tolerance intervals of 95/99 are accepted. The statistical analysis confirmed that the batches were manufactured consistently.

All batches were produced with maximum permissible hold and processing times, thus validating individual and cumulative hold times. Summaries of recent media fills were provided which were in compliance. Additionally, the Applicant conducted validation of the glass depyrogenation, equipment and component sterilisation and shipping. These validations were satisfactory, any deviations were sufficiently explained.

Manufacturing process development

For the majority of assays the IV and SC finished product are practically indistinguishable, including measurements of particulates. The only significant difference found was in turbidity, which was predictably lower for the IV product, and colour, which in light of the lower concentration and different formulation is not considered an issue.

A total of 36 SC finished product batches were used for comparative stability data at 2-8°C and compared to 6 IV finished product batches. Trend lines at the different temperatures were generally not statistically distinguishable. Turbidity was decreased for the IV finished product.

Product specification

The specification and control of excipient is sufficiently described in the dossier. All excipients are compendial (Ph. Eur.).

The attributes tested for in the finished product specification are accepted. The release specification for IV finished product includes general attributes, as well as controls for appearance, safety, purity, charge distribution, potency, and quantity.

The applicant has set out the approach to setting specifications and has given justification for each individual release criterion.

The Applicant is recommended to review all release specifications when 30 batches will have been produced.

The Applicant has given a suitable overview of the analytical procedures used and has given information about the validation of the relevant analytical procedures and also qualification summaries for the sterility and endotoxin compendial methods. The information provided is accepted and does not raise further concerns.

Analytical batch data were submitted with the dossier and demonstrate the consistency of the manufacturing process for the IV formulation: all results were in compliance and batches were consistent.

Product and process related impurities related to the finished product were characterised.

Reference standard are the same as those used for the active substance.

A sufficient description of the container closure system was provided.

Stability of the product

The Applicant has provided real time data for 8 batches of finished product (IV). Process validation batch data are available up to 9 months, whereas clinical batch data are available up to 24 months (2 batches). Following clarification regarding the history of the clinical batches, it is considered that the clinical batches are sufficiently representative of the commercial process.

The panel of analytical assays used for the determination of stability is accepted. Data demonstrate that within the 24 month period batches stay well within the defined acceptance criteria. The proposed shelf life of 24 months (2-8^{o}C) is therefore accepted.
Stability studies were supplemented with photo-stability and temperature cycling studies, the results of which raise no further questions.

The post-approval stability protocol and commitment are accepted.

Data support the in-use storage of the diluted infusion solution for up to 4 hours at room temperature.

Adventitious agents

Viral safety and the safety concerning other adventitious agents including TSE remains sufficiently assured.

2.2.4 Discussion on chemical, pharmaceutical and biological aspects

The control strategy is well presented and clear and the approach to identifying CQAs, CPP, IPCs and their respective acceptance criteria is acceptable.

Comparability data were presented to show that the IV finished product is comparable to the approved SC finished product presentation.

The manufacturing process is well described and from the data provided is under good control. Process validation data were presented from 3 batches of the commercial process and show that the process is capable of generating a product of consistent quality.

The Applicant used a statistical approach to setting finished product specifications. The proposed specifications are considered acceptable.

The Applicant provided sufficient stability data to justify the proposed shelf life of 24 months when stored at 2-8^{0}C.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Stelara concentrate for solution for infusion is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

The overall Quality of Stelara concentrate for solution for infusion is considered acceptable.

2.2.6 Recommendation for future quality development

1. The Applicant is recommended to review all release specifications when 30 batches will have been produced.

2.3. Non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Listing of Ustekinumab Clinical Studies Summarized in this Summary of Clinical Pharmacology

Study ID/Phase	Subject Population	Dose Regimen	Route of Administration	Number of Subjects Treated	Location of CSR in eCTD
CNTO1275NAP1002/ Phase 1	Healthy, normal	IV: single 6 mg/kg infusion of UST 90 mg/mL or 5 mg/mL	IV	140	Mod5.3.3.1/CNTO1275 NAP1002/CSR
C0379T07/ Phase 2a	Moderately to severely active Crohn's disease despite treatment with conventional therapy	IV: 4.5 mg/kg UST single dose SC: 90 mg UST weekly x 4	IV or SC	131	Mod5.3.5.1/C0379T07/ CSR
C0743T26/ Phase 2b	Moderately to severely active Crohn's disease who failed or were intolerant to TNF antagonist therapy	IV: 1 mg/kg, 3 mg/kg, 6 mg/kg UST or placebo at Week 0 SC: 90 mg UST or placebo at Week 8 and Week 16; 270 mg UST at Week 8[a]	IV and SC	526	Mod5.3.5.1/C0743T26/ CSR
CNTO1275CRD3001/ Phase 3 (Induction)	Moderately to severely active Crohn's disease who failed or were intolerant to TNF antagonist therapy	IV: Placebo, 130 mg, or ~6 mg/kg UST at Week 0	IV	740[b]	Mod5.3.5.1/CNTO1275 CRD3001/CSR
CNTO1275CRD3002/ Phase 3 (Induction)	Moderately to severely active Crohn's disease who were refractory to conventional therapy	IV: Placebo, 130 mg or ~6 mg/kg UST at Week 0	IV	627[c]	Mod5.3.5.1/CNTO1275 CRD3002/CSR
CNTO1275CRD3003/ Phase 3 (Maintenance)	Moderately to severely active Crohn's disease	SC: Placebo, 90 mg UST q12w or q8w IV: 130 mg UST at Week 0[d]	IV or SC	1280	Mod5.3.5.1/CNTO1275 CRD3003/W44CSR

Key: CSR=clinical study report; eCTD=electronic Common Technical Document; IV=intravenous; Mod=module; PK=pharmacokinetics; q8w=every 8 weeks; q12w=every 12 weeks; TNF=tumor necrosis factor; UST=ustekinumab; SC=subcutaneous.

[a] Subjects who did not respond to IV placebo induction therapy receive SC ustekinumab injections at Week 8 (270 mg) and at Week 16 (90 mg).

[b] Excludes 28 subjects who were enrolled before study re-start

[c] Excluded 12 subjects who enrolled before study restart

[d] Subjects who were nonresponders to placebo during an induction study (CRD3001/CRD3002) received IV ustekinumab 130 mg at Week 0 of the maintenance study (CRD3003)

The company is also conducting an extension study to study CRD3003.

2.4.2. Pharmacokinetics

The pharmacokinetics of ustekinumab following intravenous and/or subcutaneous administration were evaluated in 2 Phase 2 (C0379T07, C0743T26) and 3 Phase 3 (CNTO1275CRD3001 [CRD3001], CNTO1275CRD3002 [CRD3002], CNTO1275CRD3003 [CRD3003]) clinical studies in subjects with moderately to severely active Crohn's disease.

A Phase I study CNTO1275NAP1002 (NAP1002) where the PK of the 2 different IV formulations of ustekinumab were compared in healthy subjects in order to demonstrate PK comparability between the IV formulation used in the Phase III Crohn's disease studies and the to-be-marketed IV formulation has also been completed.

Absorption

- Bioavailability

After the intravenous induction phase of the proposed treatment of CD using ustekinumab bioavailability can be assumed to be 100%. The estimated bioavailability following SC ustekinumab administration in patients with Crohn's disease was about 78%, and the typical elimination half-life was estimated to be 19 days.

- Bioequivalence

The commercial formulation for IV induction in Crohn's disease is a dilute liquid in vial (LIV) formulation (5 mg/mL). A new 5 mg/mL formulation was subsequently developed and both biochemical and biophysical comparability was demonstrated. Study NAP1002 was conducted in healthy subjects to provide evidence of comparability for the newly developed 5 mg/mL formulation and to bridge to the 90 mg/mL formulation used in the Phase III studies.

A total of 140 subjects were randomly assigned in a 1:1 ratio to receive a 6 mg/kg IV ustekinumab infusion of either a 90 mg/mL (n=70) or 5 mg/mL (n=70) formulation. The PK profiles from the 90 mg/mL formulation used in the Phase III studies and the 5 mg/mL to-be-marketed formulation were superimposable. The formulations also demonstrated comparable PK based on the conventional bioequivalence criteria. Both formulations were well tolerated in healthy subjects and no significant or new safety findings were observed.

Distribution

The volume of distribution at steady state (Vss) is estimated to be 4.62 L which is comparable to the volume of the vascular system (5 L in a 70 kg individual), suggesting that ustekinumab is primarily distributed within the vascular system. This is consistent with the known distribution of endogenous IgG and other therapeutic mAbs. Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Elimination

Being a complex protein molecule ustekinumab can be assumed to undergo proteolysis and re-utilisation or urinary excretion of the resultant peptides and amino acids. From population pharmacokinetic analysis the typical value for clearance (CL) in a patient with an approximate body weight of 70 kg was 0.19 L/day (95% CI: 0.186 to 0.196 L/day). Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies.

The following table was obtained by the population PK analysis:

Table 8 **Ustekinumab Pharmacokinetic Parameters in Healthy Subjects and in Subjects with Crohn's Disease**

	Healthy Subjects*	Subjects with Crohn's disease**
Clearance (L/day)	0.14	0.19
Volume of distribution (L)†	4.68	4.62
Terminal Half-life (day)	24.0	18.9

*Obtained from the noncompartmental analysis (NCA) of data based on the 5 mg/mL formulation in Study NAP1002.
**Obtained from population PK analysis of data from C0743T26, CRD3002, CRD3002, and CRD3003.
†Volume of distribution based on V_z from NCA for healthy subjects, and the sum of central and peripheral volumes from the population PK analysis in subjects with Crohn's disease.

CRD PopPK Analysis Report

Dose proportionality and time dependencies

- **Dose proportionality**

Clinical Study Report C0743T26:

After a single IV administration of ustekinumab at doses of 1 mg/kg, 3 mg/kg, or 6 mg/kg, median serum ustekinumab concentrations in all treated subjects were approximately proportional to dose at all sampling timepoints through Week 8 (Figure 3).

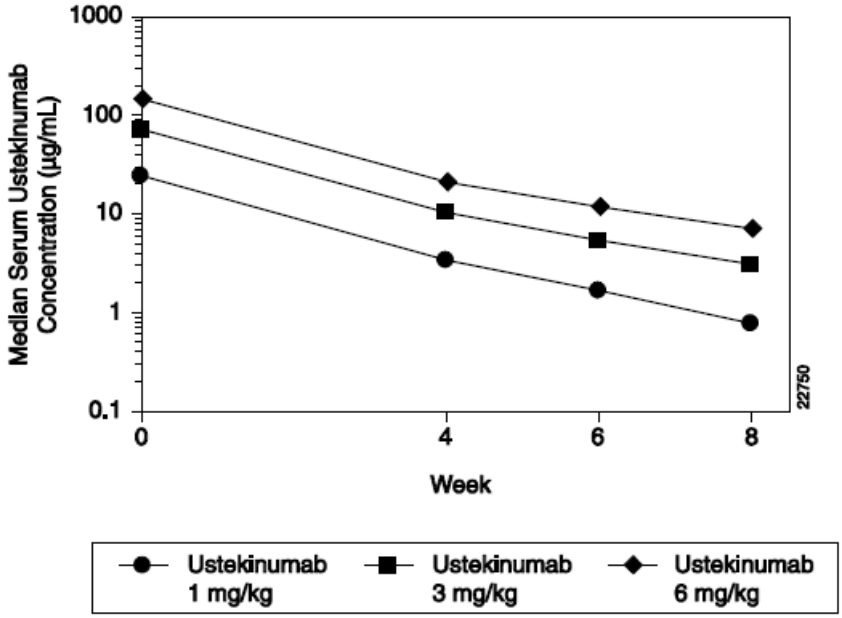


Figure 3 **Median serum ustekinumab concentrations (micrograms/mL) through Week 8; treated subjects in the induction phase**

Median peak serum ustekinumab concentrations, which were observed 1 hour after the end of infusion at Week 0, were 24.3 µg/mL, 71.6 µg/mL and 144.1 µg/mL for the 1, 3, and 6 mg/kg induction treatment groups, respectively.

At Week 6, which was the time of the primary efficacy endpoint, median serum ustekinumab concentrations were 1.7 µg/mL, 5.4 µg/mL, and 11.6 µg/mL for the 1, 3, and 6 mg/kg induction treatment groups, respectively (Table 7).

Table 7 Summary of serum ustekinumab concentrations (micrograms/mL) through Week 8; treated subjects in the induction phase

	Ustekinumab		
	1 mg/kg	3 mg/kg	6 mg/kg
Treated subjects in the induction phase	130	133	131
Week 0, preadministration			
n	127	133	130
Mean ± SD	0.46 ± 2.843	0.02 ± 0.156	0.48 ± 5.404
Median	0.00	0.00	0.00
IQ range	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)
Range	(0.0, 24.4)	(0.0, 1.6)	(0.0, 61.6)
Week 0, 1 hour postadministration			
n	123	124	123
Mean ± SD	24.97 ± 7.618	75.17 ± 22.109	152.16 ± 53.895
Median	24.30	71.57	144.10
IQ range	(19.95, 28.86)	(59.33, 86.79)	(122.68, 187.10)
Range	(0.2, 49.1)	(0.0, 134.2)	(0.0, 328.3)
Week 4			
n	107	113	107
Mean ± SD	3.51 ± 1.854	10.68 ± 5.114	22.78 ± 10.635
Median	3.39	10.33	20.73
IQ range	(2.15, 4.55)	(7.50, 14.29)	(15.28, 29.91)
Range	(0.0, 9.4)	(0.0, 24.6)	(6.2, 66.1)
Week 6			
n	106	109	104
Mean ± SD	2.12 ± 3.126	6.38 ± 3.988	12.58 ± 6.899
Median	1.66	5.36	11.64
IQ range	(0.91, 2.54)	(3.23, 8.67)	(6.76, 17.22)
Range	(0.0, 31.2)	(0.0, 18.7)	(2.1, 31.7)
Week 8, preadministration			
n	107	102	108
Mean ± SD	1.03 ± 0.849	3.86 ± 2.836	7.85 ± 5.321
Median	0.77	3.08	7.02
IQ range	(0.41, 1.52)	(1.66, 5.59)	(3.50, 11.21)
Range	(0.0, 4.1)	(0.0, 12.5)	(0.0, 22.0)

In CRD3001, median peak serum ustekinumab concentrations 1 hour after the Week 0 infusion were 43.6 µg/mL and 129.1 µg/mL for the 130 mg and ~6 mg/kg dose groups, respectively:

Table 3: Summary of Serum Ustekinumab Concentrations (micrograms/mL) through Week 8; Treated Subjects Excluding Those Enrolled Prior to Study Re-start

	Ustekinumab	
	130 mg	6 mg/kg
Analysis set: Treated subjects excluding those enrolled prior to study re-start[a]	243	245
Week 0, preadministration		
N	242	244
Mean (SD)	0.02 (0.123)	0.03 (0.288)
Median	0.00	0.00
IQ range	(0.00; 0.00)	(0.00; 0.00)
Range	(0.0; 1.1)	(0.0; 4.4)
Week 0, 1 hour postadministration		
N	230	236
Mean (SD)	43.86 (12.412)	130.40 (30.359)
Median	43.57	129.05
IQ range	(36.66; 51.18)	(111.60; 151.33)
Range	(0.0; 83.0)	(16.3; 224.8)
Week 3		
N	221	223
Mean (SD)	8.51 (3.486)	24.67 (10.036)
Median	9.03	24.18
IQ range	(5.81; 10.60)	(16.75; 32.21)
Range	(0.2; 20.1)	(0.0; 53.9)
Week 6		
N	211	211
Mean (SD)	3.74 (2.328)	10.61 (5.892)
Median	3.32	9.90
IQ range	(2.01; 5.20)	(6.41; 14.65)
Range	(0.0; 10.6)	(0.2; 32.1)
Week 8		
N	137	160
Mean (SD)	2.36 (1.778)	6.82 (4.389)
Median	2.11	6.37
IQ range	(1.00; 3.43)	(3.31; 9.60)
Range	(0.0; 8.9)	(0.0; 24.8)

[a] Subjects with pre-dose serum ustekinumab concentration ≥ 5% of the 1hr-post dose serum ustekinumab concentration are excluded.

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Study CRD3002: the corresponding peak concentrations were 39.8 µg/mL and 124.4 µg/mL for these 2 dose groups, respectively.

Table 3: Summary of Serum Ustekinumab Concentrations (micrograms/mL) through Week 8; Treated Subjects Excluding Those Enrolled Prior to Study Re-start

	Ustekinumab	
	130 mg	6 mg/kg
Analysis set: Treated subjects excluding those enrolled prior to study re-start[a]	207	206
Week 0, preadministration		
N	205	205
Mean (SD)	0.01 (0.095)	0.03 (0.221)
Median	0.00	0.00
IQ range	(0.00; 0.00)	(0.00; 0.00)
Range	(0.0; 1.3)	(0.0; 2.3)
Week 0, 1 hour postadministration		
N	197	199
Mean (SD)	40.17 (11.698)	120.74 (34.414)
Median	39.81	124.37
IQ range	(32.99; 47.26)	(101.96; 139.39)
Range	(0.0; 75.2)	(0.0; 215.5)
Week 3		
N	193	192
Mean (SD)	8.21 (3.459)	25.71 (11.206)
Median	8.04	24.68
IQ range	(6.14; 10.11)	(17.84; 32.76)
Range	(0.0; 21.9)	(0.0; 72.7)
Week 6		
N	181	182
Mean (SD)	3.93 (2.478)	11.74 (7.302)
Median	3.41	10.05
IQ range	(2.12; 5.40)	(6.85; 15.38)
Range	(0.0; 10.5)	(0.0; 45.0)
Week 8		
N	141	143
Mean (SD)	2.42 (1.701)	7.07 (4.732)
Median	2.02	6.31
IQ range	(1.18; 3.54)	(3.94; 9.58)
Range	(0.0; 7.6)	(0.0; 24.6)

[a] Subjects with pre-dose serum ustekinumab concentration ≥ 5% of the 1hr-post dose serum ustekinumab concentration are excluded.

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- **Time dependency**

Following maintenance treatment with SC ustekinumab every 8 weeks (q8w) or every 12 weeks (q12w), steady state was reached at approximately 8 or 12 weeks after subjects began receiving ustekinumab 90 mg q8w, or ustekinumab 90 mg q12w maintenance doses, respectively.
Although median serum ustekinumab concentrations 4 weeks post-dose were only slightly higher following the q8w regimen compared to those receiving the q12w regimen, median steady-state trough serum ustekinumab concentrations over time in the ustekinumab q8w group (1.97 µg/mL to 2.24 µg/mL) were 3-fold greater in the ustekinumab q8w group than in the q12w group (0.61 µg/mL to 0.76 µg/mL).
Following maintenance doses of ustekinumab 90 mg q8w or q12w, serum ustekinumab concentrations were sustained over time through Week 44 in almost all randomized subjects.

Special populations

- Impaired renal function

Ustekinumab has not been studied in impaired renal function this is clearly stated in the proposed SmPC with an additional statement that no dosage recommendation can be made.

- Impaired hepatic function

Ustekinumab has not been studied in impaired hepatic function this is clearly stated in the proposed SmPC with an additional statement that no dosage recommendation can be made.

- Elderly

No specific studies have been conducted with intravenous ustekinumab in elderly patients.

- Children

Children with Crohn's disease have not been studied. The proposed indication specifies adult CD patients.

Pharmacokinetic interaction studies

No drug – drug interactions have been performed in human populations. This is a standard situation for monoclonal antibodies and is justified on the specificity of the interaction with their ligand and that free antibody is rapidly broken down to non-functioning oligo peptide.

Immunogenicity

Among 1,154 treated patients with appropriate samples for the assessment of antibodies to ustekinumab, 27 (2.3%) were positive for antibodies to ustekinumab. Of the 27 treated patients who were positive for antibodies to ustekinumab 17 (63.0%) were positive for neutralising antibodies

The proportion of subjects who were positive for antibodies to ustekinumab among those who were receiving concomitant immunomodulators was 1.9%, compared with 2.6% of subjects who were not receiving immunomodulators. There was no apparent impact on clinical efficacy following the development of antibodies to ustekinumab. However, among those who were in clinical response to ustekinumab induction but were randomised to placebo maintenance, the remission rate was numerically lower among subjects who developed antibodies to ustekinumab (14.3%; 1 of 7) compared with the remission rate among those who were not positive for antibodies (37.1%; 46 of 124). The development of antibodies to ustekinumab had no apparent impact on injection-site reactions; however, the incidence of these events was generally low in the full study population.

2.4.3. Pharmacodynamics

Mechanism of action

IL-12 is a heterodimeric cytokine composed of four α-helices, and is involved in the differentiation of naive T-cells into Th1 cells, which is important in resistance to pathogens. It is known as a T cell stimulating factor, which can stimulate the growth and function of T cells. It stimulates the production of IFN-γ and TNF-α from T and NK cells. Ustekinumab binds to and neutralises human IL-12.

Interleukin-23 (IL-23) is a heterodimeric cytokine with a similar structure to IL-12. One of the subunits p40 is shared with IL-12, the other is p19 (the IL-23 alpha subunit). IL-23 promotes up-regulation of the matrix metalloprotease MMP9, increases angiogenesis and reduces CD8+ T-cell infiltration. In conjunction with IL-6 and TGF-β1, IL-23 stimulates naive CD4+ T cells to differentiate into a novel subset of cells called TH17, which are distinct from the classical Th1 and Th2 cells. Th17 cells produce IL-17, a proinflammatory cytokine that enhances T cell priming and stimulates the production of proinflammatory molecules. Ustekinumab binds to and neutralises human IL-23.

Primary and Secondary pharmacology

Aspects of the pharmacodynamics of ustekinumab were described in the original clinical development programme for the indication of psoriasis in 2009.

With regards to the current application:

- Plasma concentration and effect: among randomized subjects in the ustekinumab groups, greater proportions of subjects in the higher serum ustekinumab concentrations quartiles achieved efficacy endpoints compared with those in the lower serum ustekinumab concentration quartiles.
- Pharmacodynamic interactions with other described medicinal products were not found up to week 44 of exposure. Concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of Stelara In Crohn's disease studies.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics (PK) and immunogenicity of ustekinumab following intravenous (IV) and/or subcutaneous (SC) administration were evaluated in 2 Phase II (C0379T07, C0743T26) and 3 Phase III (CNTO1275CRD3001 [CRD3001], CNTO1275CRD3002 [CRD3002], CNTO1275CRD3003 [CRD3003]) clinical studies in subjects with moderately to severely active Crohn's disease. A population PK analysis and exposure-response analysis with respect to efficacy and safety, using combined data from C0743T26, CRD3001, CRD3002 and CRD3003 has been performed. The methodology utilised for conducting the population PK analysis was considered appropriate. All parameters were reasonably well estimated except the effect of immune response on clearance due to the limited sample size of subjects with positive immune response.

Ustekinumab PK parameters in healthy subjects were obtained from non-compartmental analysis, while those for subjects with Crohn's disease were obtained from the population PK analysis. Standard methodology was utilised for non-compartmental analysis. The key parameters of ustekinumab have been derived using a standard and acceptable methodology. The volume of distribution was similar between healthy subjects and subjects with Crohn's disease, clearance was lower, and T1/2 was longer in this healthy subject study compared with the studies in subjects with Crohn's disease. From the model output and covariate analysis, it is agreed that the parameter values, including covariate effects are estimated with good precision and that the model was stable and produced well-estimated parameters. In the population PK analysis of data from subjects with Crohn's disease, the impact of concomitant immunomodulators commonly used in Crohn's disease (including azathioprine, 6-mercaptoprine, methotrexate [MTX]), and corticosteroids were evaluated. There was no significant impact of any of these medications on the PK of ustekinumab in Crohn's disease which is consistent with a previous finding from a population PK analysis of ustekinumab in subjects with psoriatic arthritis (PsA), which indicated that the clearance (CL) of ustekinumab was not impacted by concomitant MTX, nonsteroidal anti-inflammatory drugs, oral corticosteroids, or prior exposure to tumor necrosis factor alpha (TNFα) antagonist agents. The use of concomitant immunomodulators with biologics (particularly TNFα-antagonists) is generally expected to result in decreased CL or increased elimination half-life, and subsequent higher systemic exposure of the biologic.

Contrary to this expectation, the median terminal elimination half-life (T1/2) in ustekinumab-treated healthy subjects (who did not receive these immunomodulators) was numerically higher than those in subjects with Crohn's disease, a signification proportion of whom were receiving immunomodulators (24.0 days vs 18.9 days). Thus, it is unlikely that the differences observed in ustekinumab

concentrations between healthy subjects and those with Crohn's disease are attributable to the impact of concomitant immunomodulators.

In the Phase III induction studies, median serum ustekinumab concentrations in patients who received induction dosing by weight (6 mg/kg) were about three-fold higher than the concentrations observed in patients who received the fixed dose induction (130 mg). Median peak serum ustekinumab concentrations 1 hour after the Week 0 infusion were 41.9 µg/mL (mean ± SD: 41.9±12.8) and 126.1 µg/mL (mean ± SD: 125.2±33.6) for the 130 mg and 6 mg/kg dose groups, respectively. Mean patient bodyweight in the studies was approximately 70 kg thus the fixed dose corresponded to approximately 2 mg/kg. At the end of induction (Week 8) in both studies, median serum ustekinumab concentrations were 2.1 µg/mL and 6.4 µg/mL for the 130 mg and 6 mg/kg dose groups, respectively.

Following maintenance treatment with ustekinumab 90 mg 8 weekly or 12 weekly in Study CRD3003, steady-state was reached by the start of the second dose. Median steady-state trough serum concentrations over time in the ustekinumab 8 weekly group (1.97 to 2.24 µg/mL) were 3-fold higher than in the 12 weekly group (0.61 to 0.76 µg/mL).

Population PK analysis indicates that body weight, serum albumin, C-reactive protein, TNF-antagonist failure status, gender, race (Asian versus non-Asian), and antibody to ustekinumab status were found to explain some of the variability observed in the PK of ustekinumab. The impact of these statistically significant covariates on the respective PK parameters was within ±20% when evaluated across a representative range of covariate values or categories in the data, which is within the overall variability observed in the PK of ustekinumab.

Based on results from Study C0743T26 it can be accepted that, following a single IV administration of ustekinumab ranging from 1 mg/kg to 6 mg/kg, median serum ustekinumab concentrations were approximately dose proportional and were detectable at all sampling time points through Week 8. Based on results submitted by the company for study 3001, it may be accepted that median peak serum ustekinumab concentrations 1 hour after the Week 0 infusion were 43.6 µg/mL and 129.1 µg/mL for the 130 mg and ~6 mg/kg dose groups, respectively. Based on results submitted by the company for study 3002, it may be accepted that median peak serum ustekinumab concentrations 1 hour after the Week 0 infusion were 39.8 µg/mL and 124.4 µg/mL for these 2 dose groups, respectively. From the clinical perspective, the company has demonstrated dose proportionality and also constant exposure over time could be shown.

The Applicant has proposed a weight-range-based dose of ustekinumab approximating 6 mg/kg (260 mg [weight ≤ 55 kg], 390 mg [weight >55 kg and 85 kg], or 520 mg [weight >85 kg]) for the induction treatment of patients with Crohn's disease. The Applicant evaluated the predicted ustekinumab exposure and the corresponding efficacy outcomes across these 3 bodyweight subgroups. Based on the PK data, ustekinumab exposures in subjects with body weight ≤ 55 kg were lower compared to those in the other bodyweight subgroups. Absolute efficacy outcomes were also lower in this subgroup as compared to the >55 kg to ≤ 85 kg, and >85 kg weight subgroups. When looking within the weight subgroups, efficacy outcomes were consistent across ustekinumab exposure quartiles in the >55 kg to 85 kg, and >85 kg weight subgroups. Within the ≤ 55 kg bodyweight subgroup, the proportion of subjects achieving efficacy outcomes were lower among subjects in the lower 2 ustekinumab exposure quartiles, while subjects in the top 2 quartiles demonstrated efficacy outcomes consistent with those in the other body weight subgroups for clinical remission. These observations suggests that approximately half of subjects in the <55 kg stratum may not have achieved optimal exposures, ie, the higher exposures associated with higher levels of efficacy. Therefore, it remains possible that targeting higher exposures in these subjects could result in greater efficacy. However, despite the lower absolute rates of efficacy in the subset of subjects in the lower 2 quartiles of the ≤ 55

kg bodyweight subgroup, the observed net treatment effects (relative to placebo) in the overall ≤ 55 kg bodyweight subgroup were generally consistent with those in the other bodyweight subgroups. Further analysis also suggests that the baseline disease characteristics of subjects in the lower 2 quartiles of the ≤ 55 kg bodyweight subgroup (higher CDAI, higher CRP, and lower albumin) may have contributed to the lower ustekinumab exposure, and lower absolute efficacy outcomes observed in this subset of subjects.

With regard to the impact of ustekinumab on body weight, this effect can be assessed from the weight component of the CDAI score. While the time period to impact weight during induction was limited, there does not appear to be an impact on the weight component of the CDAI score. For the maintenance study, this effect was assessed from the weight component of the CDAI score for change from maintenance baseline. Based on this analysis, there does not appear to be an impact of ustekinumab on the weight component, and no difference in body weight changes between the 2 active maintenance dose regimens was seen in the change from baseline during maintenance.

Although a small number of subjects developed antibodies to ustekinumab in the presented clinical studies and the effect on clearance is concluded to be small, the Applicant was requested to discuss the importance of antibody type e.g. neutralising, on the PK and the impact of immunogenicity against ustekinumab. In the corresponding ustekinumab maintenance treatment groups, there were no apparent differences in the proportions of subjects who were in clinical remission, or clinical response, at Week 44 between subjects who were positive for Nab and those who were negative for NAb. The limited number of subjects with detectable ADA does not allow a definitive conclusion on the impact of ustekinumab antibodies on the long-term efficacy of ustekinumab. The low incidence of antibodies (either neutralizing or nonneutralizing) emphasizes that the presence of ADA is not expected be a critical consideration for prescribers and patients in terms of ability to attain long-term efficacy with ustekinumab maintenance therapy.

The exposure-response relationship has shown that nonlinear logistic regression models with additive placebo and Emax drug effects on the logit-probability scale adequately described clinical responder rates at Week 6 and clinical remission rates at Week 8 and Week 52. The highest induction dose, 6 mg/kg IV and the more frequently administered maintenance dose regimen, 90 mg Q8W SC were associated with serum ustekinumab concentrations spanning the portion of the exposure response curves with the highest clinical response and remission rates.

No specific studies have been conducted with intravenous ustekinumab in elderly or paediatric patients and only 5 subjects over 75yrs age had formal PK analysis and this labelled in the SmPc which is acceptable.

2.4.5. Conclusions on clinical pharmacology

The applicant has provided sufficient data to describe the pharmacokinetics of ustekinumab. The pharmacology of ustekinumab in the treatment of Crohn's Disease is considered to be sufficiently characterized.

2.5. Clinical efficacy

2.5.1. Dose response studies

The following phase II studies were done to establish preliminary evidence of efficacy and to explore dosage and schedule.

Study C0379T07 was a Multicenter, Randomized, Phase 2a Study of Human Monoclonal Antibody to IL-12p40 (CNTO 1275) in Subjects with Moderately to Severely Active Crohn's Disease. Adult subjects with moderately to severely active Crohn's disease or fistulising Crohn's disease of at least 6 weeks duration with a Crohn's disease activity index (CDAI) score of ≥ 220 and ≤ 450 could be included. 131 subjects were randomized among 42 study sites (35 sites in the US, 6 in Canada, and 1 in Belgium).

Two populations of subjects with Crohn's disease were studied simultaneously:
Subjects in Population 1 were those with Crohn's disease despite treatment with 5-ASA compounds, antibiotics, corticosteroids, and/or immune-modulators, including anti-TNF agents. For Population 1, the design was blinded to study agent (not route of administration) and placebo-controlled. 104 subjects were randomized in Population 1, 57 male and 47 female, 90% Caucasian, ages 18-67yrs, weight 45.0-164.6Kg.

Subjects in Population 2 were those who failed to respond to, or lost response to, infliximab at the maximum approved dose and treatment regimen for Crohn's disease as defined in the US package insert. 27 subjects were randomized in Population 2, 13 male and 14 female, 85% Caucasian, ages 28-77yrs and weight 50.5-131.3Kg.

Intervention:

In Population 1, subjects were randomized to 1 of 4 treatment groups 1:1:1:1, as follows:

SC Placebo → SC CNTO 1275	Placebo subcutaneously at Weeks 0, 1, 2, and 3. At Weeks 8, 9, 10, and 11, subjects were to receive CNTO 1275 90 mg subcutaneously.
SC CNTO 1275 → SC Placebo	CNTO 1275 90 mg subcutaneously at Weeks 0, 1, 2, and 3. At Weeks 8, 9, 10, and 11, subjects were to receive placebo subcutaneously.
IV Placebo → IV CNTO 1275	Placebo intravenously at Week 0 and CNTO 1275 4.5 mg/kg intravenously at Week 8.
IV CNTO 1275 → IV Placebo	CNTO 1275 4.5 mg/kg intravenously at Week 0 and placebo intravenously at Week 8.

[CNTO 1275 is study agent]

In Population 2, approximately 20 infliximab non-responders (ie, subjects who failed to respond to, or lost response to, infliximab at the maximum approved dose and treatment regimen for Crohn's disease as defined in the US package insert) were randomized to receive open-label CNTO 1275, as follows.

- CNTO 1275 90 mg subcutaneously at Weeks 0, 1, 2, and 3
  or
- CNTO 1275 4.5 mg/kg intravenously at Week 0.

Subjects in Population 2 were not scheduled to receive placebo, and were not to receive study agent at or after Week 8. Baseline demographic characteristics were generally similar across the treatment groups.

Outcome:

Primary Efficacy Analysis: clinical response at Week 8 for Population 1.

Clinical response was defined as a reduction in the CDAI score of ≥25% and ≥70 points.

To determine the final clinical response status for a subject, treatment failure and missing data rules, as described, were applied.

The primary endpoint analysis was based on the comparison between the combined SC and IV Placebo and combined SC and IV CNTO 1275 treatment groups in Population 1. This comparison was made using a 2-sided Cochran-Mantel-Haenszel chi-square test at an 0.05 level of significance, with route of administration as the stratum.

Results are summarised in the following table:

Table 15 Number of subjects in clinical response at Week 8; randomized subjects in Population 1

	SC		IV		Combined	
	Placebo	CNTO 1275 90 mg	Placebo	CNTO 1275 4.5 mg/kg	Placebo	CNTO 1275
Subjects randomized	26	25	27	26	53	51
Subjects in clinical response[a]	13 (50.0%)	12 (48.0%)	8 (29.6%)	13 (50.0%)	21 (39.6%)	25 (49.0%)
p-value[b]		1.000		0.166		0.337

[a] Subjects who discontinued study agent due to unsatisfactory therapeutic effect, had a prohibited Crohn's disease-related surgery, or had prohibited concomitant medication changes are considered not in clinical response, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score are also considered not in clinical response.

[b] The p-value for the combined CNTO 1275 analysis is stratified by route of administration.

The proportion of subjects in clinical response at Week 8 for the SC CNTO 1275 and placebo groups was 48.0% vs 50.0%, respectively.

For the IV groups, a greater proportion of subjects in clinical response was observed at Week 8 in the CNTO 1275 group than in the Placebo group (50.0% vs 29.6%, respectively).

The company also reports on clinical response at Week 8 for Population 2

The proportion of subjects in Population 2 who were in clinical response at Week 8 was 42.9% in the SC CNTO 1275 treatment group compared with 53.8% in the IV CNTO 1275 treatment group (Table 17). These results were similar to those observed for Population 1.

Table 17 Number of subjects in clinical response at Week 8; randomized subjects in Population 2

	CNTO 1275		
	90 mg SC	4.5 mg/kg IV	Combined
Subjects randomized	14	13	27
Subjects in clinical response[a]	6 (42.9%)	7 (53.8%)	13 (48.1%)

[a] Subjects who discontinued study agent due to unsatisfactory therapeutic effect, had a prohibited Crohn's disease-related surgery, or had prohibited concomitant medication changes are considered not in clinical response, regardless of their CDAI score. Subjects who had insufficient data to calculate the CDAI score are also considered not in clinical response.

C0743T26 was a multicentre, randomised, double-blind study of ustekinumab IV induction followed by SC maintenance in subjects with moderately to severely active Crohn's disease who had previously failed TNF antagonist therapy. The study was designed to confirm the Phase 2a study results and identify the IV induction dose and SC maintenance dose regimens to be carried into Phase III.

Patients had a diagnosis of moderately to severely active Crohn's disease of at least three months duration with a CDAI score of ≥ 220 and ≤ 450. Patients had received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of Crohn's disease, and either did not respond initially, lost response, or were intolerant to the medication (according to predefined failure criteria).

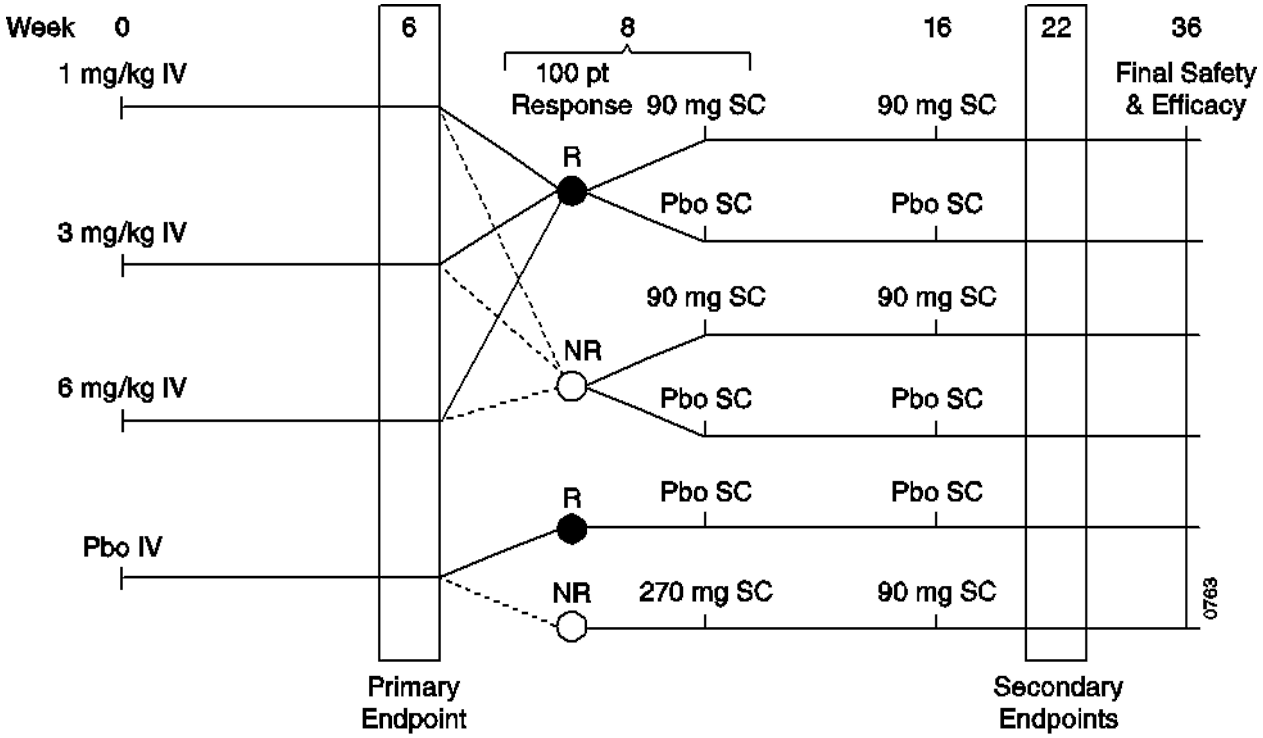
At the Week 0 visit, 526 patients were randomised in a 1:1:1:1 ratio to a single IV infusion of placebo or ustekinumab 1, 3, or 6 mg/kg. A dynamic randomisation procedure using a minimisation algorithm with investigative site and initial response to TNF antagonist therapy (yes or no) as the stratification variables was used. At Week 6, all patients were evaluated for the primary endpoint of clinical response. Patients continued to be followed for induction efficacy to Week 8.

The study also included a maintenance phase. At Week 8, responders and non-responders to IV ustekinumab were separately re-randomised in a 1:1 ratio to either ustekinumab or placebo. Inclusion in the responder or non-responder groups was based on clinical response status at Week 6 (clinical response was defined as a reduction from baseline in CDAI of ≥ 100 points or <150 for patients with a baseline score ≥ 220 to ≤ 248, also referred to as 100-point response). These patients received ustekinumab 90 mg SC or placebo SC at Weeks 8 and 16, and were assessed for efficacy at Week 22. Patients who were randomised to placebo induction dosing were not re-randomised at Week 8; those in clinical response to IV placebo induction dosing at Week 6 continued to receive placebo SC injections

at Weeks 8 and 16 and those who were not in clinical response to IV placebo induction dosing at Week 6 received ustekinumab 270 mg SC at Week 8 and 90 mg SC at Week 16.

Patients receiving oral corticosteroids at Week 0 who were in clinical response at Week 6 were to have their daily dose of corticosteroids tapered by the investigator beginning at Week 8.

A diagram of the full study design is shown in Figure 1.



R = responder, NR = nonresponder

Efficacy Results

The proportion of patients in clinical response (100-point response) at Week 6 (primary endpoint) was significantly greater in the 6 mg/kg group (39.7%) than in the placebo group (23.5%, p=0.005). There did not appear to be a dose response relationship between the three ustekinumab groups.

The effect of ustekinumab on inducing clinical response was generally consistent across subgroups by demographics, baseline disease characteristics, concomitant medications at baseline and Crohn's disease-related drug history, and by anti-TNF therapy history (data not shown here).

In the maintenance phase of the study patients randomised as responders to ustekinumab IV induction, and who received ustekinumab SC 90 mg at Weeks 8 and 16, significant benefit was observed in clinical remission and clinical response at Week 22 (Table 3 below).

Table	**Efficacy results clinical outcomes, induction phase, randomised patients C0743T26**				
	Placebo	Ustekinumab 1 mg/kg	Ustekinumab 3 mg/kg	Ustekinumab 6 mg/kg	Combined Ustekinumab
N	132	131	132	131	394

Clinical response (100-point response)					
Week 4 (Major Secondary Endpoint)	16.7%	27.5%*	37.1%*	30.5%*	31.7%*
Week 6 (Primary Endpoint)	23.5%	36.6%*	34.1%	39.7%*	36.8%*
Week 8	17.4%	32.1%*	31.8%*	43.5%*	35.8%*
Clinical remission					
Week 4	9.1%	10.7%	18.9%*	12.2%	14.0%
Week 6 (Major Secondary Endpoint)	10.6%	16.0%	15.9%	12.2%	14.7%
Week 8	10.6%	17.6%	18.2%	18.3%	18.0%*
Baseline CDAI mean (median)	312.4 (302.5)	318.5 (306.0)	326.8 (327.0)	338.0 (333.0)	327.7 (324.0)
CDAI change from baseline (median)					
Week 4	-14.0	-47.0*	-54.0*	-52.0*	-50.0*
Week 6	-29.5	-53.0*	-59.0*	-65.0*	-60.0*
Week 8	-23.0	-55.0*	-54.5*	-81.0*	-64.0*

*Nominal p-value <0.05 for active vs placebo comparison.
CDAI=Crohn's Disease Activity Index; N=subject number.

Table 3 Key efficacy results, maintenance phase, based on all patients randomised as responders to ustekinumab induction in C0743T26

	Placebo SC	Ustekinumab 90 mg SC
Subjects randomised as responders to ustekinumab induction	73	72
Clinical remission at Week 22 (major secondary endpoint)	27.4%	41.7%, p = 0.029
Clinical response at Week 22	42.5%	69.4%, p < 0.001
Sustained clinical response through Week 22	32.9%	55.6%, p = 0.005
Remission at Week 22 among subjects in clinical remission at Week 6	53.3% (16/30)	78.6% (22/28), p = 0.056
Clinical remission and not receiving corticosteroids at Week 22 (corticosteroid-free remission)	17.8%	30.6%, p = 0.048

Induction dose

The induction dose was based on results of the phase 2 studies:

- The SC regimen in study C0379T07 returned results that were not different to placebo and so the iv regimens were pursued in the C0743T26 Phase 2b study.
- 1 mg/kg, 3 mg/kg, and 6 mg/kg doses were chosen for study C0743T26 based on modelling and indications that a high dose of 6 mg/kg would lead to higher efficacy.

The following doses were selected for the Phase 3 induction studies:

- An ustekinumab 130 mg IV fixed dose was chosen for the low-dose group (~2 mg/kg was thought to be sufficient to overcome the observation that 1 mg/kg may have lost effectiveness between Weeks 6 and 8) in C0743T26.

- The high dose ustekinumab group was based on tiered dosing by weight at multiples of 130 mg IV vial approximating 6 mg/kg IV (<55 kg: 260 mg ustekinumab; >55 kg to ≤85 kg: 390 mg ustekinumab; >85 kg: 520 mg ustekinumab).

Given that the tiered dosing by weight was at multiples of 130 mg, the 130 mg IV vial would minimize the potential for dosing errors and, because this presentation contained the exact dose intended for delivery, it would both minimize waste and eliminate the potential for inappropriate use of leftover product in these vials intended for single use.

Maintenance dose

A SC route of administration was chosen based upon greater convenience and the premise that treatment by the SC route would maintain response and remission.

A maintenance regimen of ustekinumab 90 mg SC q8w was selected based on the observation that subjects in response in C0379T07 demonstrated a tendency to lose their clinical response when serum ustekinumab concentrations decreased below 1 - 2 µg/mL. Based on PK modelling, the 90 mg q8w regimen was predicted to provide a steady-state serum trough level of 1.69 µg/mL. Results up to 22 weeks in study C0743T26 also supported the Q8W dose.

The ustekinumab 90 mg SC q12w regimen was predicted to achieve a steady-state trough concentration of about 0.4 µg/mL and had been studied extensively in psoriasis and thought likely to also succeed in maintaining response and remission in Crohn's disease.

2.5.2. Main studies

Studies CRD3001 and CRD3002 were near replicate with the same methodology Stelara common to both studies. The principal difference was the CD population which in the 3001 study were required to have failed on or been intolerant of previous anti-TNF therapy while in the 3002 study they may, or may not, have received previous anti-TNF therapy but should not have failed on or been intolerant to it. Therefore only the results sections of the 3002 study are described below while a full description of Study 3001 is given.

CRD3001: A Phase III, Randomised, Double-blind, Placebo-controlled, Parallel-group, Multicentre Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients with Moderately to Severely Active Crohn's Disease who have failed or are Intolerant to TNF Antagonist Therapy.

CRD3002. A Phase III, Randomised, Double-blind, Placebo-controlled, Parallel-group, Multicentre Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients with Moderately to Severely Active Crohn's Disease.

Methods

Study Participants

Inclusion criteria

- Men or women aged 18 years or older at the time of informed consent with moderately to severely active Crohns disease (of at least 3 months duration), with colitis, ileitis, or ileocolitis, confirmed by radiography, histology, and/or endoscopy. Active disease was defined as a CDAI score ≥ 220 but ≤ 450.
- Subjects had to have received infliximab (REMICADE®), adalimumab (HUMIRA®), or certolizumab pegol (CIMZIA®) at a dose approved for the treatment of Crohn's disease and either did not respond initially, responded initially but then lost response, or were intolerant to the medication
- Subjects had to meet criteria for concomitant medication stability, screening laboratory test results, and TB history and testing results, and had to agree to use adequate birth control measures.
- Subjects had to allow a washout period of at least 8 weeks for prior TNF antagonist use.

- Subjects had to adhere to the following requirements for concomitant medication for the treatment of Crohn's disease. The following medications are permitted provided doses meeting the requirements below are stable for or have been discontinued at least 3 weeks prior to baseline (Week 0), unless otherwise specified:
    a. Oral 5-ASA compounds.
    b. Oral corticosteroids (eg, prednisone, budesonide) at a prednisone-equivalent dose of ≤40 mg/day or ≤9 mg/day of budesonide.
    c. Antibiotics being used as a primary treatment of Crohn's disease.
    d. Subjects receiving conventional immunomodulators (ie, AZA, 6-MP, or MTX) must have been taking them for ≥ 12 weeks, and on a stable dose for a least 4 weeks prior to baseline.

- Subjects had to have screening laboratory test results within the following parameters:
    a. Haemoglobin ≥8.5 g/dL
    b. WBCs ≥3.5 x 103/µL
    c. Neutrophils ≥1.5 x 103/µL
    d. Platelets ≥100 x 103/µL
    e. Serum creatinine < 1.7 mg/dL
    f. AST and ALT concentrations must be within 2 times the ULN range for the laboratory conducting the test.
    g. Direct (conjugated) bilirubin < 1.0 mg/dL.

Exclusion criteria

- Complications of Crohn's disease that might require surgery or preclude the use of the CDAI to assess response
- had a functioning stoma or ostomy
- prior treatment with any therapeutic agent targeted at reducing IL-12 or IL-23
- organ transplantation
- known substance abuse within 12 months
- evidence of active or latent infection or history of infection, as described
- malignancy
- severe, progressive or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease
- Within stated time periods before baseline:
    - had or were suspected to have an abscess within 8 weeks
    - had any kind of bowel resection within 3 months or diversion or any other intra-abdominal surgery within 6 months
    - had a stool culture or other examination that was positive for an enteric pathogen within 4 months
    - received non-autologous stem cell therapy within 12 months, iv corticosteroid, immunomodulatory agents (other than azathioprine, 6-mercaptopurine, or methotrexate) within 12 weeks, biologic agents within 8 weeks, investigational drugs within 4 weeks, and treatment with apheresis or total parenteral nutrition within 3 weeks
    - Bacille Calmette-Guérin vaccination within 12 months or any other live vaccine within 12 weeks

Treatments

Subjects were to be randomized in a 1:1:1 ratio to receive a single IV administration of either placebo or 1 of 2 induction doses of ustekinumab at Week 0:

- Group 1: Placebo
- Group 2: Ustekinumab 130 mg
- Group 3: Tiered ustekinumab doses approximating ustekinumab 6 mg/kg:
    - Ustekinumab 260 mg (weight ≤55 kg)
    - Ustekinumab 390 mg (weight >55 kg and ≤85 kg)
    - Ustekinumab 520 mg (weight >85 kg)

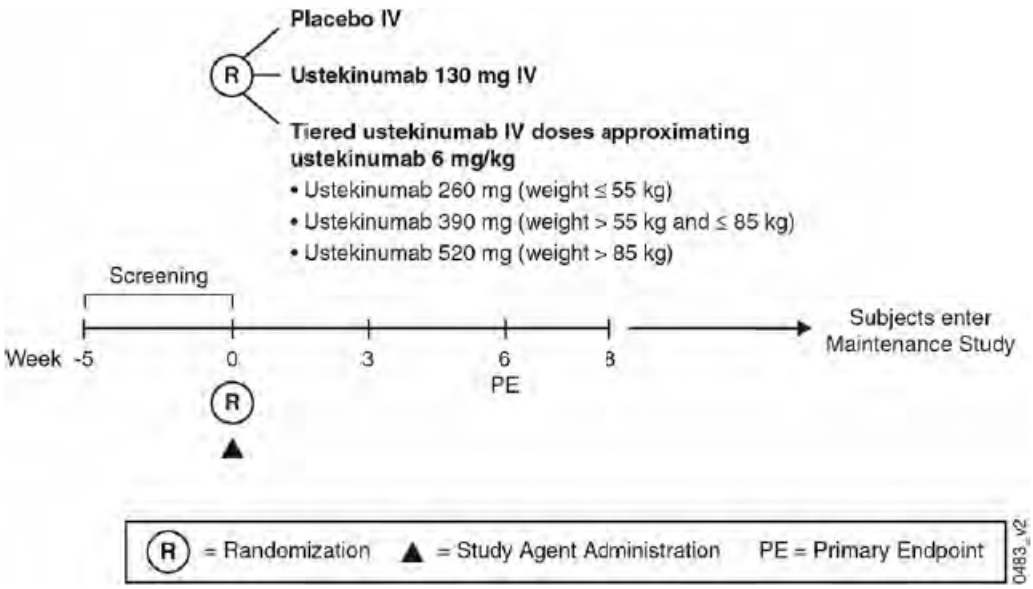
At Week 6, all subjects were to be evaluated for the primary endpoint of clinical response.

At Week 8, subjects who had been randomized to ustekinumab induction therapy at Week 0 and had been induced into clinical response at Week 8 in this study were eligible to enter the maintenance study, CNTO1275CRD3003, as the primary efficacy population.
Subjects who were not in clinical response to ustekinumab induction therapy, as well as all subjects who initially received placebo (both in clinical response and not in clinical response), were also eligible

to enter Study CNTO1275CRD3003 at Week 8, but were not included in the primary efficacy population.

A diagrammatic representation of the study design is shown in the following figure:

Figure 1: Study design



Subjects who did not enter the maintenance study were to have a safety follow-up visit approximately 20 weeks after the Week 0 study agent administration.

Objectives

Primary Objectives

- To evaluate the efficacy of IV induction regimens of ustekinumab in inducing clinical response in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to one or more TNF antagonist therapies.
- To evaluate the safety of IV induction regimens of ustekinumab in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to one or more TNF antagonist therapies.

Secondary Objectives

- To evaluate the efficacy of IV induction regimens of ustekinumab in inducing clinical remission.
- To evaluate the efficacy of IV induction regimens of ustekinumab in improving disease-specific health-related quality of life.
- To evaluate the pharmacokinetics and pharmacodynamics of ustekinumab therapy, including changes in CRP, fecal calprotectin, fecal lactoferrin, and other pharmacodynamic biomarkers.
- To provide, along with induction study CNTO1275CRD3002, the target study population to be evaluated in the maintenance study CNTO1275CRD3003

Outcomes/endpoints

Primary endpoint

Clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥100 points. Subjects with a baseline CDAI score of ≥220 to ≤248 points were considered to be in clinical response if a CDAI score of <150 was attained.

Major secondary endpoints

In order of importance:

1) clinical remission at Week 8, defined as a CDAI score <150 points
2) clinical response at Week 8
3) 70-point response at Week 6, defined as a reduction from baseline in the CDAI score of ≥70 points
4) 70-point response at Week 3

Efficacy evaluations included

- the Crohn's Disease Activity Index
- serum CRP concentrations
- stool samples analyses for fecal lactoferrin and fecal calprotectin markers
- the Inflammatory Bowel Disease Questionnaire and the 36-Item Short-Form Health Survey
- Fistula closure (assessed for subjects with fistula disease) and reduction or resolution of lesions was to be assessed for subjects with pyoderma gangrenosum.
- Mucosal healing was to be assessed by ileo-colonoscopy at participating sites in subjects who consented to participate in that sub-study.
- Health economics analyses were also to be performed.

Safety assessment was to be based on reported adverse events, clinical laboratory test results, vital sign measurements, physical examinations, electrocardiogram findings, and tuberculosis testing. Blood samples were taken for pharmacokinetic and pharmacodynamic evaluations.

Sample size

CRD3001: Assuming a 25% clinical response rate at Week 6 in the placebo group and a 40% rate in the ustekinumab high dose group, 205 subjects per treatment group were predicted to yield an overall power of 90%, at a significance level of 0.05 (2-sided).

The power for detecting a significant difference between the ustekinumab high dose group and placebo was also examined for the first major secondary endpoint of clinical remission at Week 8. Assuming a 10% clinical remission rate at Week 8 in the placebo group, and a rate of 20% in the ustekinumab high-dose group, 205 subjects per treatment group were predicted to yield an overall power of 81%, at a significance level of 0.05 (2-sided). To increase the power to detect a significant difference for the clinical remission endpoint, the sample size for the key efficacy analyses was increased to 225 subjects per treatment group (total sample size of 675), which provides 85% power for the clinical remission endpoint.

Randomisation

Subjects were to be allocated to 1 of 3 treatment groups using a permuted block randomization with study region (Asia, Eastern Europe, or rest of world), CDAI score (≤300 or >300), and initial response to TNF antagonist therapy (yes or no) as the stratification variables.
For subjects who had received multiple TNF antagonist therapies, their initial response status (yes or no) was to be determined by whether they initially responded to the first TNF antagonist therapy received.
Allocation to treatment group was performed using a central randomization centre by means of an IVRS/IWRS.

Blinding (masking)

The study was double-blinded. To maintain the study blind, the study agent container was to have a multilingual label containing the study name, medication number, and reference number. A tear-off label was designed to be separated from the study agent container and attached to the subject's source documents; the label was not to identify the study agent in the container. The medication number was to be entered in the case report form (CRF) when the study agent was dispensed. Study agents were packaged so as to be identical in appearance in order to maintain the study blind.

Statistical methods

Handling Missing Data

The CDAI score was calculated for a visit only if 4 or more of the 8 components were available at that visit. When at least 4 of the 8 components were available, any missing components were imputed by carrying forward the last non-missing component, with the exception of a missing hematocrit value where the value obtained closest to the date of the visit (before or after) was used if it was within 7 days, otherwise the last observation was carried forward.

If the CDAI score could not be calculated (i.e., <4 components available) at a visit, the CDAI score was considered missing. Subjects with a missing CDAI score at Week 6 were considered to not have achieved clinical response at Week 6.

Analysis Method

The proportion of subjects in clinical response at week 6 was compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran-Mantel-Haenszel chi-square test, stratified by study region (Asia, Eastern Europe, or rest of world) and baseline CDAI score (≤300 or >300) at a significance level of 0.05. Initial response to TNF antagonist therapy (yes or no) was an additional stratification factor in CRD3001.

Control of Type I Error Rate

A fixed sequence testing procedure was used to control the overall Type 1 error rate at the 0.05 level of significance. Specifically, the ustekinumab high dose group (dose approximating 6 mg/kg ustekinumab) was first compared with the placebo group at the 2-sided 0.05 level of significance. If the ustekinumab high dose group was significantly different from the placebo group, then the ustekinumab low dose group (130 mg ustekinumab) was compared with the placebo group at the 2-sided 0.05 level of significance.

The study was considered to be positive if the ustekinumab high dose group was significantly different from the placebo group for the primary endpoint.

Sensitivity Analyses

To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint were conducted using the observed case, last observation carried forward, multiple imputation, and the worst case (missing=success on placebo and failure on active) missing data methods Treatment failure rules were to override the missing data rules, meaning that if a subject has both an event of treatment failure (ie, a Crohn's disease-related surgery thought to be a result of lack of efficacy of study agent or specified changes in concomitant Crohn's disease medications) before Week 6 and has a missing CDAI score at Week 6 (i.e., <4 components of the CDAI available), the subject was considered a nonresponder in the sensitivity analysis regardless of whether or not CDAI data are present.

A sensitivity analysis in which subjects who were randomized but never treated were excluded was also performed.

Datasets for Analysis

Efficacy: Efficacy analyses included subjects randomized at Week 0. Efficacy analyses were to be based on an intent-to-treat principle. Therefore, the efficacy data for each subject were analyzed according to the assigned treatment, regardless of the actual treatment received.

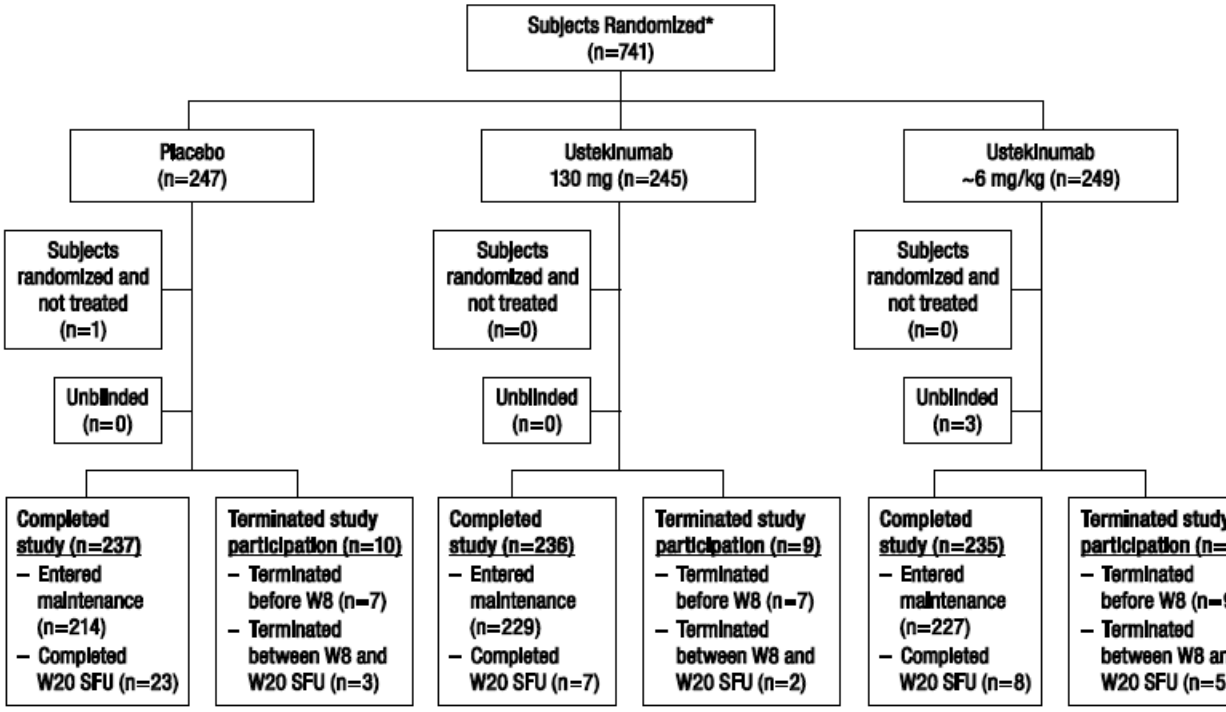
Clinical Pharmacology and Safety: Unless otherwise specified, the PK analyses were based on subjects who received at least 1 dose of IV ustekinumab, and safety analyses were based on subjects who received at least 1 dose of IV study agent. Subjects were analyzed according to the actual treatment received.

Results (study CRD3001)

Participant flow

Subjects were randomly assigned in a 1:1:1 ratio to receive a single IV administration of placebo (n=247) or 1 of 2 induction doses of ustekinumab at Week 0: 130 mg ustekinumab (n=245) or tiered ustekinumab doses approximating 6 mg/kg (~6 mg/kg ustekinumab group; n=249), as shown in the following diagram:

Figure 2: Subject disposition in Study CNTO1275CRD3001: Randomized subjects excluding those enrolled prior to study re-start



Recruitment

Study centres: 178 sites in North America, Europe, the Asia-Pacific region, Israel, South Africa and Brazil.

Start of study: 23rd June 2011. Completion of study: 3rd July 2013

Conduct of the study

The protocol deviations reported were adequately addressed and did not compromise the validity of the study nor affected the overall interpretation of the clinical study. Amendments were not considered to have affect study validity.

Baseline data

Subject baseline demographic characteristics are summarized in the following table:

Table 2: Summary of Demographics at Baseline; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/kg[a]	Ustekinumab Combined	Total
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494	741
Age (years)					
N	247	245	249	494	741
Mean (SD)	37.3 (11.83)	37.4 (11.77)	37.3 (12.54)	37.4 (12.15)	37.3 (12.04)
Median	36.0	37.0	36.0	36.0	36.0
IQ range	(27.0; 46.0)	(27.0; 45.0)	(26.0; 45.0)	(27.0; 45.0)	(27.0; 45.0)
Range	(18; 71)	(18; 70)	(18; 71)	(18; 71)	(18; 71)
Sex					
N	247	245	249	494	741
Male	118 (47.8%)	98 (40.0%)	101 (40.6%)	199 (40.3%)	317 (42.8%)
Female	129 (52.2%)	147 (60.0%)	148 (59.4%)	295 (59.7%)	424 (57.2%)
Race					
N	247	245	249	494	741
White	210 (85.0%)	202 (82.4%)	211 (84.7%)	413 (83.6%)	623 (84.1%)
Black or African American	8 (3.2%)	7 (2.9%)	8 (3.2%)	15 (3.0%)	23 (3.1%)
Asian	20 (8.1%)	20 (8.2%)	23 (9.2%)	43 (8.7%)	63 (8.5%)
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Other	5 (2.0%)	6 (2.4%)	3 (1.2%)	9 (1.8%)	14 (1.9%)
Not Reported	4 (1.6%)	8 (3.3%)	4 (1.6%)	12 (2.4%)	16 (2.2%)
Unknown	0	2 (0.8%)	0	2 (0.4%)	2 (0.3%)
Weight (kg)					
N	247	245	249	494	741
Mean (SD)	71.51 (17.738)	68.44 (17.401)	69.46 (19.463)	68.95 (18.458)	69.80 (18.249)
Median	69.10	65.90	66.00	66.00	67.00
IQ range	(57.50; 82.60)	(55.80; 77.50)	(56.00; 79.30)	(55.90; 78.00)	(56.70; 80.00)
Range	(35.0; 141.8)	(35.3; 124.0)	(35.0; 172.8)	(35.0; 172.8)	(35.0; 172.8)
Height (cm)					
N	247	245	249	494	741
Mean (SD)	170.65 (9.539)	168.70 (9.425)	169.66 (9.375)	169.18 (9.403)	169.67 (9.468)
Median	170.00	168.00	169.30	168.90	169.00
IQ range	(163.00; 176.50)	(162.00; 175.00)	(163.00; 175.50)	(162.60; 175.30)	(162.60; 175.50)
Range	(149.3; 197.0)	(147.3; 196.0)	(142.4; 196.0)	(142.4; 196.0)	(142.4; 197.0)

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

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Baseline demographic characteristics were similar across the treatment groups.

4.5% of subjects did not complete the study: 3.1% terminated before Week 8 and 1.3% of subjects terminated between Week 8 and the Week 20 safety follow-up visit. The most common reason for termination was withdrawal of consent.

Baseline Disease Characteristics are summarised in the following table:

TSIDEM03: Summary of Crohn's Disease Characteristics at Baseline; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/kg[a]	Combined	Total
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494	741
Crohn's disease duration (yrs)					
N	246	245	249	494	740
Mean (SD)	12.13 (8.414)	11.79 (8.324)	12.69 (9.246)	12.24 (8.803)	12.21 (8.670)
Median	9.69	9.90	10.97	10.28	10.14
IQ range	(6.00; 16.69)	(5.14; 15.90)	(5.80; 17.83)	(5.41; 16.46)	(5.62; 16.65)
Range	(0.5; 45.0)	(0.5; 40.1)	(0.1; 51.9)	(0.1; 51.9)	(0.1; 51.9)
Involved GI areas					
N	246	245	249	494	740
Ileum only	28 (11.4%)	38 (15.5%)	37 (14.9%)	75 (15.2%)	103 (13.9%)
Colon only	48 (19.5%)	36 (14.7%)	40 (16.1%)	76 (15.4%)	124 (16.8%)
Ileum and colon	166 (67.5%)	171 (69.8%)	171 (68.7%)	342 (69.2%)	508 (68.6%)
Proximal gastrointestinal tract	45 (18.3%)	57 (23.3%)	54 (21.7%)	111 (22.5%)	156 (21.1%)
Perianal	107 (43.5%)	107 (43.7%)	107 (43.0%)	214 (43.3%)	321 (43.4%)
Extra intestinal involvement					
N	246	245	249	494	740
Any extra intestinal manifestations	121 (49.2%)	127 (51.8%)	128 (51.4%)	255 (51.6%)	376 (50.8%)
Arthritis/arthralgia	112 (45.5%)	122 (49.8%)	116 (46.6%)	238 (48.2%)	350 (47.3%)
Iritis/uveitis	6 (2.4%)	7 (2.9%)	8 (3.2%)	15 (3.0%)	21 (2.8%)
E. nodosum	3 (1.2%)	3 (1.2%)	11 (4.4%)	14 (2.8%)	17 (2.3%)
Pyoderma gangrenosum	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Aphthous stomatitis	12 (4.9%)	10 (4.1%)	9 (3.6%)	19 (3.8%)	31 (4.2%)
PSC	2 (0.8%)	2 (0.8%)	3 (1.2%)	5 (1.0%)	7 (0.9%)
CDAI score					
N	247	245	249	494	741
Mean (SD)	319.0 (59.67)	321.0 (64.67)	327.6 (62.02)	324.4 (63.37)	322.6 (62.17)
Median	313.0	318.0	319.0	319.0	317.0
IQ range	(272.0; 356.0)	(270.0; 357.0)	(276.0; 372.0)	(274.0; 366.0)	(274.0; 360.0)
Range	(198; 515)	(198; 512)	(210; 498)	(198; 512)	(198; 515)
IBDQ score (32-224)					
N	244	243	248	491	735
Mean (SD)	120.0 (29.27)	119.5 (29.47)	118.2 (26.64)	118.8 (28.06)	119.2 (28.45)
Median	120.0	120.0	118.0	119.0	120.0
IQ range	(99.0; 140.0)	(98.0; 138.0)	(98.0; 138.0)	(98.0; 138.0)	(98.0; 138.0)
Range	(60; 202)	(51; 185)	(57; 198)	(51; 198)	(51; 202)
CRP (mg/L)					
N	247	245	249	494	741
Mean (SD)	16.56 (21.064)	19.96 (24.792)	19.50 (25.347)	19.73 (25.049)	18.67 (23.827)
Median	8.53	10.40	9.93	10.15	9.88
IQ range	(3.38; 21.90)	(3.48; 26.60)	(3.72; 26.60)	(3.55; 26.60)	(3.48; 24.40)
Range	(0.1; 180.0)	(0.1; 157.0)	(0.1; 145.0)	(0.1; 157.0)	(0.1; 180.0)
Crohn's Disease Complications					
N	247	245	249	494	741
Intra-abdominal abscess (Past)	34 (13.8%)	32 (13.1%)	38 (15.3%)	70 (14.2%)	104 (14.0%)
Sinus tracts / perforation[b]	16 (6.5%)	21 (8.6%)	22 (8.8%)	43 (8.7%)	59 (8.0%)
Fistula[b]	127 (51.4%)	113 (46.1%)	112 (45.0%)	225 (45.5%)	352 (47.5%)
Current	53 (21.5%)	43 (17.6%)	47 (18.9%)	90 (18.2%)	143 (19.3%)
Bowel Stricturing[b]	108 (43.7%)	109 (44.5%)	115 (46.2%)	224 (45.3%)	332 (44.8%)
Current	20 (8.1%)	29 (11.8%)	23 (9.2%)	52 (10.5%)	72 (9.7%)

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Current or past.

Disease characteristics were balanced across the 3 treatment groups. Furthermore Medical history and current diagnoses as well as concomitant medications were balanced across the treatment groups. Among the subset of subjects who had failed corticosteroids, the proportion was slightly higher in the ~6 mg/kg group (51.0%) compared with the placebo and 130 mg groups (41.5% and 37.8%, respectively). This difference was not expected to affect study results.
The proportions of subjects who had previously received immunomodulators and had failed or become intolerant to them were balanced across the treatment groups.

To enter the study, subjects had to have previously failed at least 1 TNF antagonist (ie infliximab, adalimumab, or certolizumab pegol), either by having an inadequate initial response, by having a response following by loss of response, or by being intolerant. Subjects could have met more than 1 of these criteria.

TNF antagonist therapy history is summarized in the following tables:

TSICM03: Summary of TNF Antagonist Therapy History by Number of TNF Antagonists Received; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/kg[a]	Combined	Total
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494	741
Subjects with inadequate initial response	74 (30.0%)	70 (28.6%)	72 (28.9%)	142 (28.7%)	216 (29.1%)
1 TNF antagonist	59 (23.9%)	61 (24.9%)	64 (25.7%)	125 (25.3%)	184 (24.8%)
2 TNF antagonists	15 (6.1%)	9 (3.7%)	8 (3.2%)	17 (3.4%)	32 (4.3%)
3 TNF antagonists	0	0	0	0	0
Subjects with response followed by loss of response	170 (68.8%)	173 (70.6%)	171 (68.7%)	344 (69.6%)	514 (69.4%)
1 TNF antagonist	112 (45.3%)	111 (45.3%)	124 (49.8%)	235 (47.6%)	347 (46.8%)
2 TNF antagonists	52 (21.1%)	57 (23.3%)	39 (15.7%)	96 (19.4%)	148 (20.0%)
3 TNF antagonists	6 (2.4%)	5 (2.0%)	8 (3.2%)	13 (2.6%)	19 (2.6%)
Subjects with intolerance	87 (35.2%)	78 (31.8%)	105 (42.2%)	183 (37.0%)	270 (36.4%)
1 TNF antagonist	69 (27.9%)	65 (26.5%)	87 (34.9%)	152 (30.8%)	221 (29.8%)
2 TNF antagonists	17 (6.9%)	11 (4.5%)	15 (6.0%)	26 (5.3%)	43 (5.8%)
3 TNF antagonists	1 (0.4%)	2 (0.8%)	3 (1.2%)	5 (1.0%)	6 (0.8%)
Subjects with inadequate initial response, loss of response, or intolerance	246 (99.6%)	243 (99.2%)	246 (98.8%)	489 (99.0%)	735 (99.2%)
1 TNF antagonist	112 (45.3%)	124 (50.6%)	120 (48.2%)	244 (49.4%)	356 (48.0%)
2 TNF antagonists	108 (43.7%)	92 (37.6%)	102 (41.0%)	194 (39.3%)	302 (40.8%)
3 TNF antagonists	26 (10.5%)	27 (11.0%)	24 (9.6%)	51 (10.3%)	77 (10.4%)

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

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Among all subjects, 29.1% had an inadequate initial response, 69.4% had response followed by loss of response, and 36.4% had intolerance to 1 or more TNF antagonists; 48.0% had failed 1 TNF antagonist in the past and approximately half had failed 2 or 3 TNF antagonists (40.8% and 10.4%, respectively).

78.8% of subjects had failed infliximab, 59.8% had failed adalimumab and 22.1% had failed certolizumab pegol. The TNF history was balanced across all groups.

Numbers analysed

The primary efficacy analyses were conducted in the primary analysis population. Subjects were analysed according to the treatment group to which they were randomized: 247 subjects to placebo, 245 to 130mg, 249 to 6mg/kg.

Outcomes and estimation

Primary Efficacy Analysis

The primary endpoint was clinical response at Week 6, as defined, and as shown in the following table:

Table 6: Number of Subjects in Clinical Response at Week 6; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

		Ustekinumab		
	Placebo	130 mg	6 mg/kg[a]	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494
Week 6				
N	247	245	249	494
Subjects in clinical response[b,c]	53 (21.5%)	84 (34.3%)	84 (33.7%)	168 (34.0%)
p-value		0.002	0.003	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight >85 kg).
[b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at Week 6 are considered not to be in clinical response.

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A significantly greater proportion of subjects in the ~6 mg/kg ustekinumab and 130 mg ustekinumab groups were in clinical response at Week 6 (33.7% and 34.3%, respectively) compared with the placebo group (21.5%; p=0.003 and p=0.002, respectively). The study met its primary end-point.

4% (31/741) of randomized subjects had missing data for the CDAI score at Week 6 (5.3%, 5.2%, and 2.0% of subjects in the placebo, ~6 mg/kg, and 130 mg ustekinumab groups, respectively). Sensitivity analyses supported the main analysis.

Major Secondary Analyses

Clinical remission at Week 8 was defined as a CDAI score of <150 points. Results are shown in the following table:

Table 7: Number of Subjects in Clinical Remission at Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

		Ustekinumab		
	Placebo	130 mg	6 mg/kg[a]	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494
Week 8				
N	247	245	249	494
Subjects in clinical remission[b,c]	18 (7.3%)	39 (15.9%)	52 (20.9%)	91 (18.4%)
p-value		0.003	< 0.001	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical remission, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at Week 8 are considered not to be in clinical remission.

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The proportion of subjects in remission at Week 8 was numerically greater in the ~6 mg/kg dose group than in the 130 mg group.
Results for clinical response at Week 8 are shown in the following table:

Table 8: Number of Subjects in Clinical Response at Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

	Placebo	130 mg	Ustekinumab 6 mg/kg[a]	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494
Week 8				
N	247	245	249	494
Subjects in clinical response[b,c]	50 (20.2%)	82 (33.5%)	94 (37.8%)	176 (35.6%)
p-value		0.001	< 0.001	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to Week 8 are considered not to be in clinical response, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at Week 8 are considered not to be in clinical response.

[TEFCRES03.rtf] [CNTO1275\CRD3001\DBR_W8_W20\RE_W8_W20\tefcres.sas] 16AUG2013, 16:00

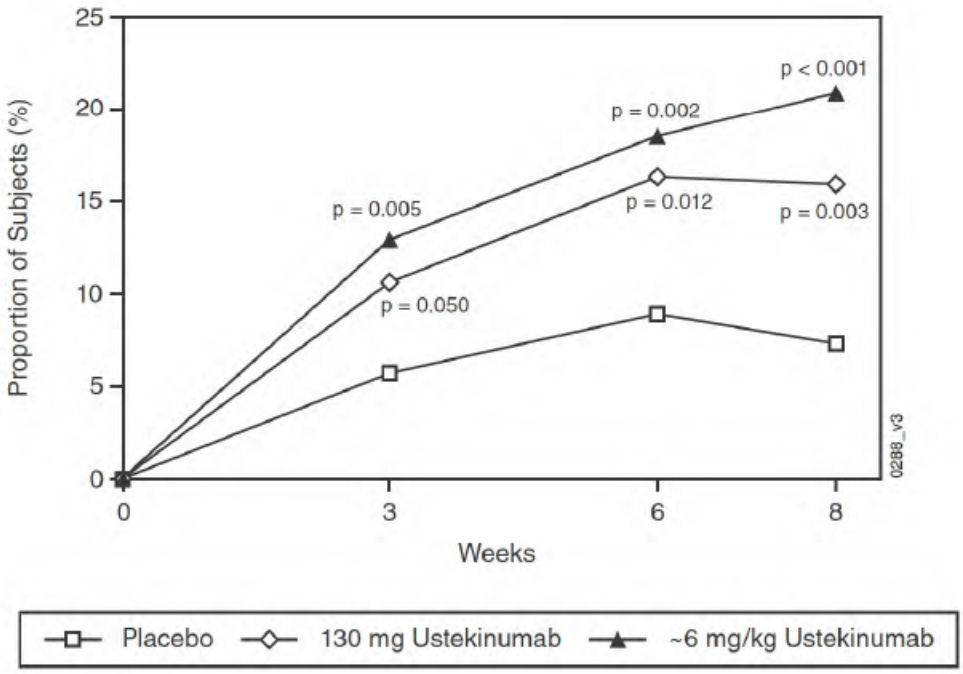
A significantly greater proportion of subjects in the ~6 mg/kg ustekinumab and 130 mg ustekinumab groups were in 70-point response at Week 3 (40.6% and 38.4%, respectively) compared with the placebo group (27.1%; p=0.001 and p=0.009, respectively).

The endpoint of 70-point response at Week 6 was defined as a reduction from baseline in the CDAI score of ≥70 points at Week 6. A significantly greater proportion of subjects in the ~6 mg/kg ustekinumab and 130 mg ustekinumab groups were in 70-point response at Week 6 (43.8% and 46.1%, respectively) compared with the placebo group (30.4%; p=0.002 and p<0.001, respectively).

Ancillary analyses

The proportions of subjects in clinical remission through Week 8 are shown in the following figure:

Figure 4: Number of Subjects in Clinical Remission through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start



[a] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical remission, regardless of their CDAI score.

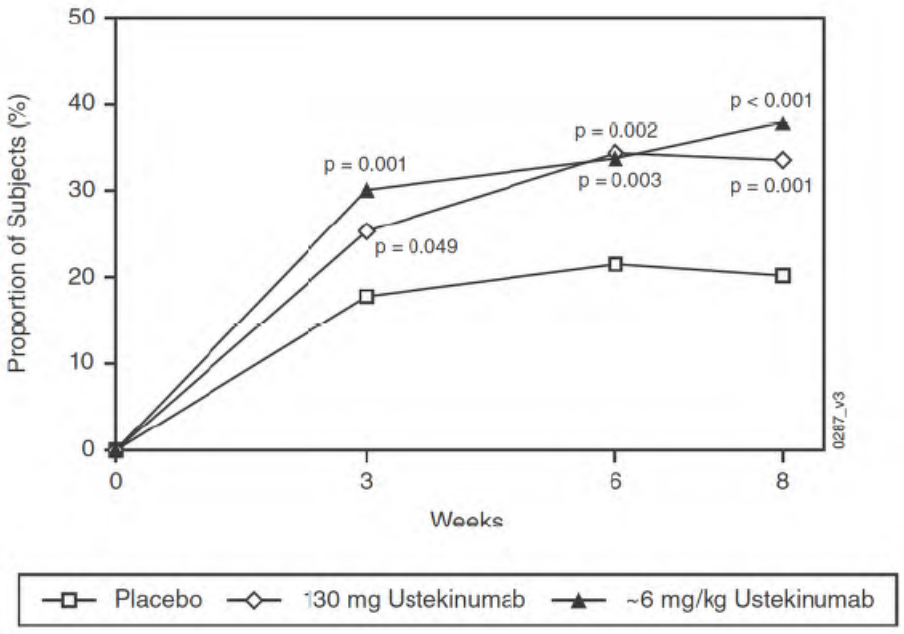
[b] Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical remission.

Data source: [TEFCREM02.rtf] [CNTO1275\CRD3001\DBR_W8_W20\RE_W8_W20\tefcrem02.sas] 16AUG2013, 16:00

The proportion of subjects in clinical remission was apparent from week 3.

The proportions of subjects in clinical response through Week 8 are shown in the following figure:

Figure 5: Number of Subjects in Clinical Response through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start



[a] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response, regardless of their CDAI score.

[b] Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response.

Data source: [TEFCRES06.rtf] [CNTO1275\CRD3001\DBR_W8_W20\RE_W8_W20\tefcres06.sas] 16AUG2013, 16:01

Summary of main study(ies)

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

Summary of Efficacy for trial CRD3001

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy			
Study identifier	CRD3001		
Design	Randomised, double-blind, placebo-controlled multicentre study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 weeks not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Ustekinumab 130mg		Single IV administration of ustekinumab; randomized n=245
	Ustekinumab 6mg/kg		Single IV administration of ustekinumab; randomized n=249
	Placebo		Single IV administration of placebo; randomized n=247
Endpoints and definitions	Primary endpoint	Clinical Response at week 6	Reduction from baseline in the CDAI score of ≥100 points or to <150 at week 6
	Major Secondary endpoint	Clinical Remission at week 8	CDAI score <150 at week 8

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat – all patients randomized after study re-start			
Descriptive statistics and estimate variability	Treatment group	Ustekinumab 130mg	Ustekinumab 6mg/kg	Placebo
	Number of subjects	245	249	247
	Clinical response rate at week 6	84 (34.3%)	84 (33.7%)	53 (21.5%)

Effect estimate per comparison		Comparison groups	Ustekinumab 130mg vs. placebo
		P-value	p=0.002
		Comparison groups	Ustekinumab 6mg/kg vs. placebo
		P-value	p=0.003

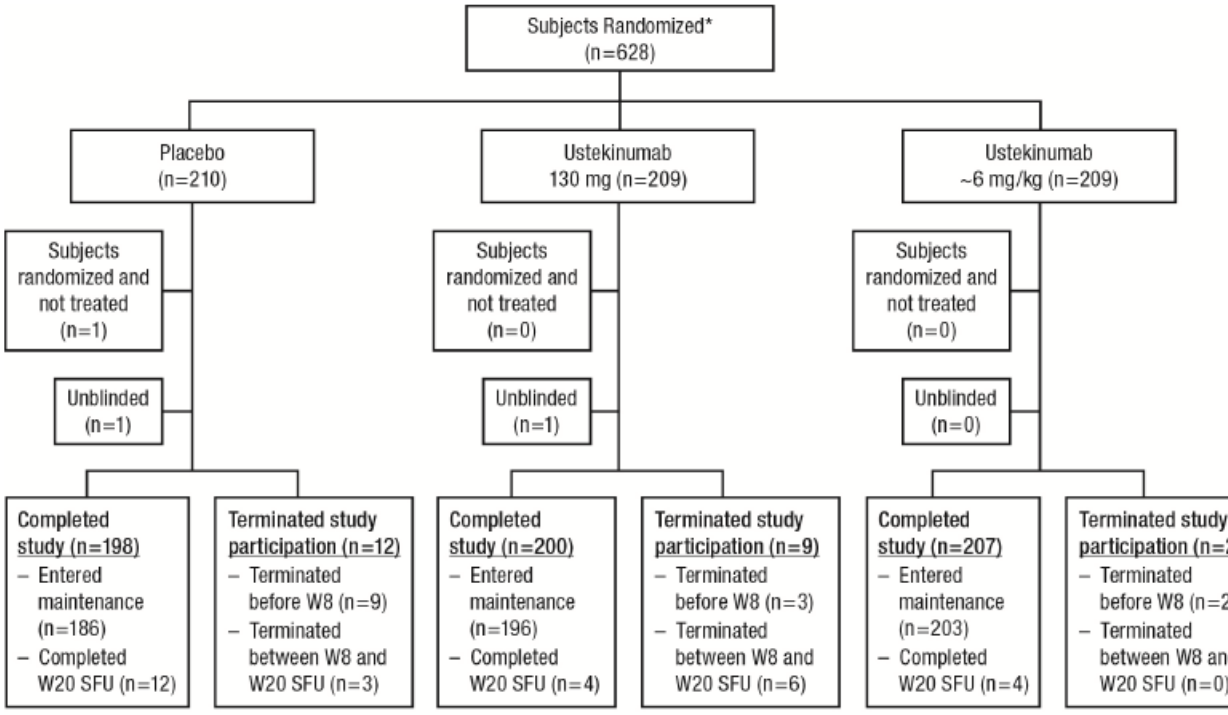
Analysis description	**Major Secondary Endpoint**			
Analysis population and time point description	Intent to treat – all patients randomized after study re-start			
Descriptive statistics and estimate variability	Treatment group	Ustekinumab 130mg	Ustekinumab 6mg/kg	Placebo
	Number of subjects	245	249	247
	Clinical remission at week 8	39 (15.9%)	52 (20.9%)	18 (7.3%)
		Comparison groups	Ustekinumab 130mg vs. placebo	
		P-value	p=0.003	
		Comparison groups	Ustekinumab 6mg/kg vs. placebo	
		P-value	p<0.001	

Results (Study CRD3002)

Participant flow

Subjects were randomly assigned in a 1:1:1 ratio to receive a single IV administration of placebo (n=210) or 1 of 2 induction doses of ustekinumab at Week 0: ustekinumab 130 mg (n=209) or tiered ustekinumab doses approximating 6 mg/kg (ustekinumab ~6 mg/kg; n=209), as shown in the following diagram:

Figure 2: Subject disposition in Study CNTO1275CRD3002: Randomized subjects excluding those enrolled prior to study re-start



*Excludes subjects randomized before study restart; SFU=safety follow-up.

Recruitment

Subjects were recruited at 175 sites in North America, South America, Eastern Europe, Western Europe, Asia Pacific, and South Africa.
Study started: 23rd June 2011. Study completed: 28th October 2014

Conduct of the study

Protocol deviations reported were adequately handled and did not compromise the validity of the study nor affected the overall interpretation of the clinical study. Amendments were not considered to have affect study validity.

Baseline data

Of the 628 randomized subjects, baseline demographics were balanced across the treatment groups, as shown in the following table:

Table 2: Summary of Demographics at Baseline; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

		Ustekinumab			
	Placebo	130 mg	6 mg/kg[a]	Combined	Total
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	210	209	209	418	628
Age (years)					
N	210	209	209	418	628
Mean (SD)	40.2 (13.10)	39.1 (13.78)	38.4 (13.12)	38.7 (13.45)	39.2 (13.34)
Median	39.0	37.0	36.0	36.0	37.0
IQ range	(30.0; 50.0)	(28.0; 49.0)	(27.0; 49.0)	(28.0; 49.0)	(29.0; 49.0)
Range	(18; 77)	(18; 75)	(18; 74)	(18; 75)	(18; 77)
Sex					
N	210	209	209	418	628
Male	99 (47.1%)	104 (49.8%)	90 (43.1%)	194 (46.4%)	293 (46.7%)
Female	111 (52.9%)	105 (50.2%)	119 (56.9%)	224 (53.6%)	335 (53.3%)
Race					
N	210	209	209	418	628
White	177 (84.3%)	175 (83.7%)	174 (83.3%)	349 (83.5%)	526 (83.8%)
Black or African American	7 (3.3%)	6 (2.9%)	7 (3.3%)	13 (3.1%)	20 (3.2%)
Asian	17 (8.1%)	17 (8.1%)	16 (7.7%)	33 (7.9%)	50 (8.0%)
American Indian or Alaska Native	0	0	1 (0.5%)	1 (0.2%)	1 (0.2%)
Native Hawaiian or other Pacific Islander	0	0	2 (1.0%)	2 (0.5%)	2 (0.3%)
Other	7 (3.3%)	10 (4.8%)	6 (2.9%)	16 (3.8%)	23 (3.7%)
Not Reported	0	1 (0.5%)	3 (1.4%)	4 (1.0%)	4 (0.6%)
Unknown	2 (1.0%)	0	0	0	2 (0.3%)
Weight (kg)					
N	210	209	209	418	628
Mean (SD)	74.02 (19.919)	74.36 (21.329)	71.87 (18.825)	73.11 (20.130)	73.41 (20.049)
Median	70.00	70.50	71.70	70.90	70.80
IQ range	(60.20; 85.40)	(59.00; 85.00)	(58.00; 82.30)	(58.00; 84.00)	(58.70; 84.10)
Range	(40.0; 155.6)	(37.0; 184.0)	(35.0; 154.0)	(35.0; 184.0)	(35.0; 184.0)
Height (cm)					
N	210	209	209	418	628
Mean (SD)	169.68 (9.700)	170.93 (9.939)	168.73 (9.923)	169.83 (9.980)	169.78 (9.880)
Median	169.55	172.00	168.20	170.00	170.00
IQ range	(161.50; 177.00)	(164.00; 177.00)	(161.50; 175.30)	(162.60; 177.00)	(162.60; 177.00)
Range	(139.7; 195.0)	(144.0; 198.1)	(147.0; 195.6)	(144.0; 198.1)	(139.7; 198.1)

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

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Baseline disease characteristics were balanced across the 3 groups, as shown in the following table:

TSIDEM03: Summary of Crohn's Disease Characteristics at Baseline; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/kg[a]	Ustekinumab Combined	Total
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	210	209	209	418	628
Crohn's disease duration (yrs)					
N	210	209	209	418	628
Mean (SD)	10.37 (9.831)	8.69 (8.462)	8.68 (8.436)	8.68 (8.439)	9.25 (8.956)
Median	8.28	5.61	6.21	5.82	6.40
IQ range	(2.39; 13.98)	(2.42; 12.25)	(2.01; 12.50)	(2.13; 12.46)	(2.22; 13.07)
Range	(0.3; 52.4)	(0.3; 47.1)	(0.3; 43.2)	(0.3; 47.1)	(0.3; 52.4)
Involved GI areas					
N	210	208	209	417	627
Ileum only	44 (21.0%)	53 (25.5%)	49 (23.4%)	102 (24.5%)	146 (23.3%)
Colon only	37 (17.6%)	44 (21.2%)	43 (20.6%)	87 (20.9%)	124 (19.8%)
Ileum and colon	129 (61.4%)	109 (52.4%)	117 (56.0%)	226 (54.2%)	355 (56.6%)
Proximal gastrointestinal tract	32 (15.2%)	34 (16.3%)	29 (13.9%)	63 (15.1%)	95 (15.2%)
Perianal	57 (27.1%)	60 (28.8%)	61 (29.2%)	121 (29.0%)	178 (28.4%)
Extra intestinal involvement					
N	210	209	209	418	628
Any extra intestinal manifestations	120 (57.1%)	113 (54.1%)	116 (55.5%)	229 (54.8%)	349 (55.6%)
Arthritis/arthralgia	114 (54.3%)	108 (51.7%)	108 (51.7%)	216 (51.7%)	330 (52.5%)
Iritis/uveitis	11 (5.2%)	5 (2.4%)	2 (1.0%)	7 (1.7%)	18 (2.9%)
E. nodosum	6 (2.9%)	4 (1.9%)	10 (4.8%)	14 (3.3%)	20 (3.2%)
Pyoderma gangrenosum	0	1 (0.5%)	3 (1.4%)	4 (1.0%)	4 (0.6%)
Aphthous stomatitis	13 (6.2%)	7 (3.3%)	11 (5.3%)	18 (4.3%)	31 (4.9%)
PSC	0	2 (1.0%)	0	2 (0.5%)	2 (0.3%)
CDAI score					
N	210	209	209	418	628
Mean (SD)	302.2 (61.67)	304.1 (56.97)	302.2 (58.85)	303.1 (57.86)	302.8 (59.11)
Median	289.5	294.0	286.0	293.0	292.5
IQ range	(254.0; 339.0)	(257.0; 340.0)	(257.0; 342.0)	(257.0; 342.0)	(257.0; 341.0)
Range	(204; 608)	(208; 465)	(198; 459)	(198; 465)	(198; 608)
IBDQ score (32-224)					
N	208	208	207	415	623
Mean (SD)	122.4 (31.45)	118.2 (30.99)	122.8 (31.62)	120.5 (31.35)	121.1 (31.37)
Median	120.0	115.5	124.0	121.0	121.0
IQ range	(102.0; 144.0)	(95.0; 144.0)	(99.0; 148.0)	(96.0; 146.0)	(98.0; 146.0)
Range	(49; 193)	(46; 189)	(56; 195)	(46; 195)	(46; 195)
CRP (mg/L)					
N	210	209	209	418	628
Mean (SD)	15.03 (16.827)	15.25 (21.381)	17.52 (24.139)	16.39 (22.803)	15.93 (20.990)
Median	8.50	7.38	7.82	7.71	8.05
IQ range	(3.22; 21.70)	(3.07; 19.40)	(3.75; 21.10)	(3.39; 19.80)	(3.34; 20.25)
Range	(0.1; 93.3)	(0.1; 124.0)	(0.1; 137.0)	(0.1; 137.0)	(0.1; 137.0)
Crohn's Disease Complications					
N	210	209	209	418	628
Intra-abdominal abscess (Past)	25 (11.9%)	17 (8.1%)	22 (10.5%)	39 (9.3%)	64 (10.2%)
Sinus tracts / perforation[b]	12 (5.7%)	14 (6.7%)	9 (4.3%)	23 (5.5%)	35 (5.6%)
Fistula[b]	77 (36.7%)	69 (33.0%)	74 (35.4%)	143 (34.2%)	220 (35.0%)
Current	33 (15.7%)	34 (16.3%)	31 (14.8%)	65 (15.6%)	98 (15.6%)
Bowel Stricturing[b]	74 (35.2%)	63 (30.1%)	58 (27.8%)	121 (28.9%)	195 (31.1%)
Current	25 (11.9%)	25 (12.0%)	16 (7.7%)	41 (9.8%)	66 (10.5%)

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Current or past

The median Crohn's disease duration was slightly higher in the placebo group at baseline (8.28 years) compared with the ustekinumab groups (5.61 years and 6.21 years in 130 mg and ~6 mg/kg group, respectively).

Relevant Medical History is summarised in the following table:

TSIMH01: Summary of Medical History and Current Diagnoses (Including Cardiovascular Disease History) at Baseline; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

		Ustekinumab			
	Placebo	130 mg	6 mg/kg[a]	Combined	Total
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	210	209	209	418	628
Psoriasis	15 (7.1%)	16 (7.7%)	21 (10.0%)	37 (8.9%)	52 (8.3%)
Psoriatic arthritis	3 (1.4%)	4 (1.9%)	3 (1.4%)	7 (1.7%)	10 (1.6%)
Congestive heart failure	1 (0.5%)	0	2 (1.0%)	2 (0.5%)	3 (0.5%)
Subject had current or past ASCVD	7 (3.3%)	6 (2.9%)	10 (4.8%)	16 (3.8%)	23 (3.7%)
Peripheral vascular disease	4 (1.9%)	1 (0.5%)	4 (1.9%)	5 (1.2%)	9 (1.4%)
Transient ischemic attack	1 (0.5%)	1 (0.5%)	2 (1.0%)	3 (0.7%)	4 (0.6%)
Stroke	2 (1.0%)	2 (1.0%)	0	2 (0.5%)	4 (0.6%)
Ischemic heart/coronary artery disease	3 (1.4%)	3 (1.4%)	4 (1.9%)	7 (1.7%)	10 (1.6%)
Subjects who had cardiovascular risk factors	98 (46.7%)	88 (42.1%)	86 (41.1%)	174 (41.6%)	272 (43.3%)
Hyperlipidemia	13 (6.2%)	9 (4.3%)	15 (7.2%)	24 (5.7%)	37 (5.9%)
Hypertension	39 (18.6%)	28 (13.4%)	32 (15.3%)	60 (14.4%)	99 (15.8%)
Diabetes mellitus	11 (5.2%)	9 (4.3%)	7 (3.3%)	16 (3.8%)	27 (4.3%)
Family history of early coronary artery disease	10 (4.8%)	14 (6.7%)	13 (6.2%)	27 (6.5%)	37 (5.9%)
Current smoking	61 (29.0%)	51 (24.4%)	45 (21.5%)	96 (23.0%)	157 (25.0%)
Subjects who had two or more cardiovascular risk factors	27 (12.9%)	17 (8.1%)	19 (9.1%)	36 (8.6%)	63 (10.0%)

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

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Overall, medical history and current diagnoses were balanced across the treatment groups as well as the proportion of subjects receiving each class of Crohn's disease medication at baseline was similar across the 3 treatment groups.

96.3% of subjects had previously received corticosteroids with approximately 81% of subjects having previously failed, become intolerant of, or been dependent on, corticosteroids.

Approximately 75% of subjects had been treated with a full and adequate course of immunomodulators in the past, and approximately 68% of subjects had either failed or become intolerant to immunomodulators.

Subjects in the study were allowed to have previously received TNF antagonists, but they were not to have demonstrated inadequate response or intolerance to them. The subjects included those who were naive to TNF antagonists.

Numbers analysed

Per protocol, all subjects were to receive 1 dose of study agent at Week 0.

Subjects were analysed according to the treatment group to which they were randomized: 209 subjects to placebo, 209 to 130mg, 209 to 6mg/kg.

Efficacy analyses were based on an intent-to-treat principle.

Outcomes and estimation

Primary Efficacy Analysis

The primary endpoint was clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥100 points. Subjects with a baseline CDAI score of ≥220 to ≥248 points were

considered to be in clinical response if a CDAI score of <150 was attained. Results are shown in the following table:

Table 6: Number of Subjects in Clinical Response at Week 6; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127

	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/kg[a]	Ustekinumab Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start and excluding site 1127	209	209	209	418
Week 6				
N	209	209	209	418
Subjects in clinical response[b,c]	60 (28.7%)	108 (51.7%)	116 (55.5%)	224 (53.6%)
p-value		< 0.001	< 0.001	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight >85 kg).
[b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at Week 6 are considered not to be in clinical response.

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2.6% (n=16) of randomized subjects had a missing CDAI score at Week 6 (8 [3.8%], 3 [1.4%], and 5 [2.4%] of subjects in the placebo, ~6 mg/kg, and 130 mg ustekinumab groups, respectively. Sensitivity analyses were consistent with the primary analysis.

Major Secondary Analyses

Clinical remission at Week 8 was defined as a CDAI score of <150 points. Results are summarised in the following table:

Table 7: Number of Subjects in Clinical Remission at Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127

	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/kg[a]	Ustekinumab Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start and excluding site 1127	209	209	209	418
Week 8				
N	209	209	209	418
Subjects in clinical remission[b,c]	41 (19.6%)	64 (30.6%)	84 (40.2%)	148 (35.4%)
p-value		0.009	< 0.001	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to Week 8 are considered not to be in clinical remission, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at Week 8 are considered not to be in clinical remission.

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A significantly greater proportion of subjects in both the ustekinumab ~6 mg/kg and ustekinumab 130 mg groups were in clinical remission at Week 8 (40.2% and 30.6%, respectively) compared with the placebo group (19.6%; p<0.001 and p=0.009, respectively.

Clinical Response at Week 8 is summarised in the following table:

Table 8: Number of Subjects in Clinical Response at Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127

	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/kg[a]	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start and excluding site 1127	209	209	209	418
Week 8				
N	209	209	209	418
Subjects in clinical response[b,c]	67 (32.1%)	99 (47.4%)	121 (57.9%)	220 (52.6%)
p-value		< 0.001	< 0.001	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes prior to Week 8 are considered not to be in clinical response, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at Week 8 are considered not to be in clinical response.

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A significantly greater proportion of subjects in both the ustekinumab ~6 mg/kg and ustekinumab 130 mg groups were in clinical response at Week 8 (57.9% and 47.4%, respectively) compared with the placebo group (32.1%; p<0.001 for both).

A significantly greater proportion of subjects in both the ustekinumab ~6 mg/kg and ustekinumab 130 mg groups were in 70-point response at Week 3 (50.7% and 49.3%, respectively) compared with the placebo group (31.6%; p<0.001 for both).

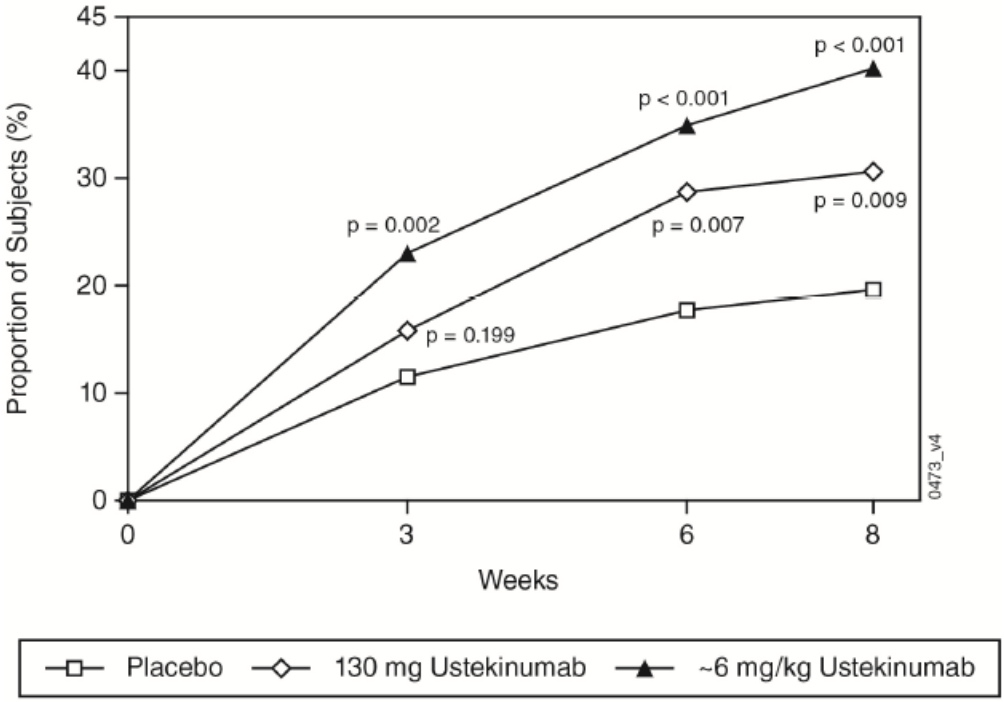
The endpoint of 70-point response at Week 6 was defined as a reduction from baseline in the CDAI score of ≥70 points at Week 6. A significantly greater proportion of subjects in both the ustekinumab ~6 mg/kg and ustekinumab 130 mg groups were in 70-point response at Week 6 (64.6% and 58.9%, respectively) compared with the placebo group (38.8%; p<0.001 for both).

Additional analyses:

Clinical remission over time

A higher proportion of subjects in clinical remission when on study drug was evident from week 3, as shown in the following figure:

Figure 4: **Number of Subjects in Clinical Remission through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127**



[a] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical remission, regardless of their CDAI score.

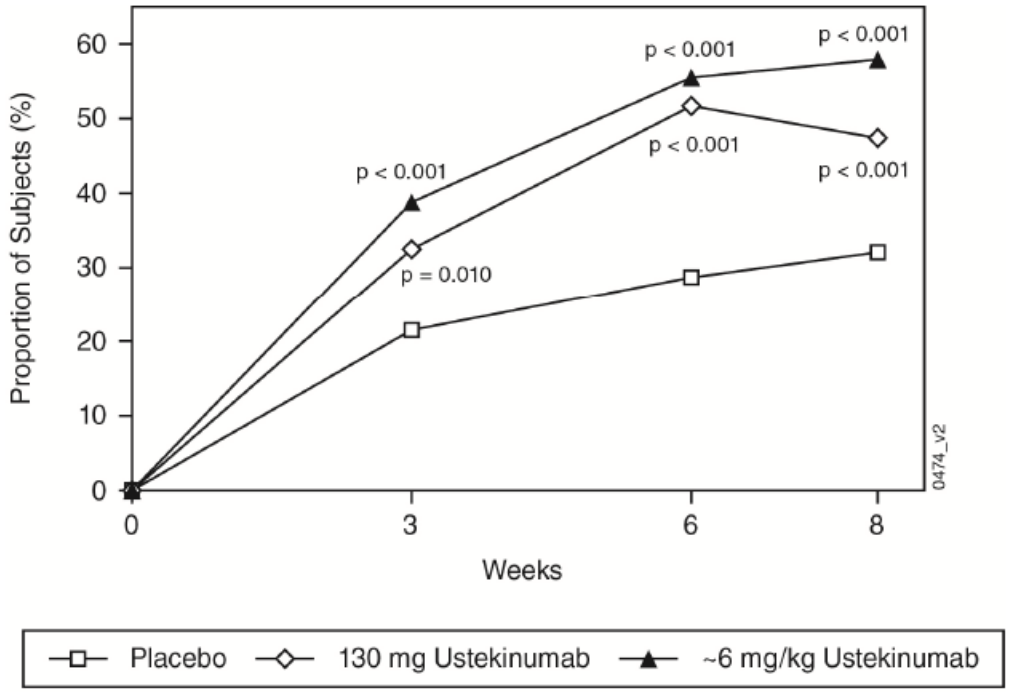
[b] Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical remission.

Data Source: [TEFCREM02.rtf] [CNTO1275\CRD3002\DBR_W20\RE_W20\tefcrem02.sas] 26NOV2014, 16:32

Clinical response over time

A higher proportion of subjects in clinical response when on study drug was evident from week 3, as shown in the following figure:

Figure 5: Number of Subjects in Clinical Response through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127



[a] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response, regardless of their CDAI score.

[b] Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response.

Data Source: [TEFCRES06.rtf] [CNTO1275\CRD3002\DBR_W20\RE_W20\tefcres06.sas] 26NOV2014, 16:32

Summary of main study(ies)

The following table summarises the efficacy results from the study 3002 supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table E2. Summary of efficacy for trial CRD3002

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease		
Study identifier	CRD3002	
Design	Randomised, double-blind, placebo-controlled multicentre study	
	Duration of main phase: Duration of Run-in phase:	8 weeks not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Ustekinumab 130mg		Single IV administration of ustekinumab; randomized n=209
	Ustekinumab 6mg/kg		Single IV administration of ustekinumab; randomized n=209
	Placebo		Single IV administration of placebo; randomized n=210
Endpoints and definitions	Primary endpoint	Clinical Response at week 6	Reduction from baseline in the CDAI score of ≥100 points or to <150 at week 6
	Major Secondary endpoint	Clinical Remission at week 8	CDAI score <150 at week 8

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat – all patients randomized after study re-start excluding site 1127			
Descriptive statistics and estimate variability	Treatment group	Ustekinumab 130mg	Ustekinumab 6mg/kg	Placebo
	Number of subjects	209	209	209
	Clinical response rate at week 6	108 (51.7%)	116 (55.7%)	60 (28.7%)
Effect estimate per comparison		Comparison groups	Ustekinumab 130mg vs. placebo	
		P-value	p<0.001	
		Comparison groups	Ustekinumab 6mg/kg vs. placebo	
		P-value	p<0.001	

Analysis description	**Major Secondary Endpoint**			
Analysis population and time point description	Intent to treat – all patients randomized after study re-start excluding site 1127			
Descriptive statistics and estimate variability	Treatment group	Ustekinumab 130mg	Ustekinumab 6mg/kg	Placebo
	Number of subjects	209	209	209
	Clinical remission at week 8	64 (30.6%)	84 (40.2%)	41 (19.6%)
		Comparison groups	Ustekinumab 130mg vs. placebo	
		P-value	p=0.009	
		Comparison groups	Ustekinumab 6mg/kg vs. placebo	
		P-value	p<0.001	

CRD3003: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease

Methods

Study Participants

Primary Population

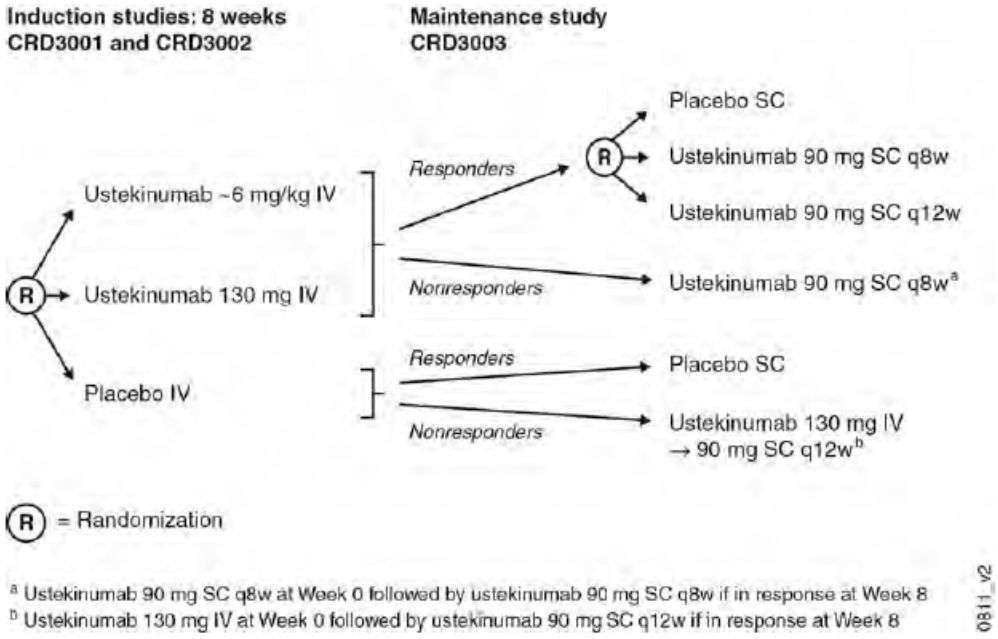
The primary population for the key efficacy analyses is those subjects in clinical response to IV ustekinumab induction therapy (at Week 8 of the induction studies, CNTO1275CRD3001 and CNTO1275CRD3002).

Other Subject Populations Entering This Study

- Subjects in clinical response to IV placebo (at Week 8 of the induction studies, CNTO1275CRD3001 and CNTO1275CRD3002)
- Subjects not in clinical response to IV ustekinumab (at Week 8 of the induction studies, CNTO1275CRD3001 and CNTO1275CRD3002)
- Subjects not in clinical response to IV placebo (at Week 8 of the induction studies, CNTO1275CRD3001 and CNTO1275CRD3002)

Flow of subjects is summarised in the following diagram:

Figure 3: Flow of subjects from induction studies CRD3001 and CRD3002 into maintenance study CRD3003



Subjects who were not in the primary population were to be followed for both efficacy and safety and received additional study agent as described below, but were not be included in the key efficacy analyses.

Treatments

Primary Population:

Subjects in Clinical Response to Ustekinumab Induction Dosing

Subjects will be randomized in a 1:1:1 ratio at Week 0 of this maintenance study to receive 1 of the following SC regimens.

- Group 1: Placebo
- Group 2: Ustekinumab 90 mg SC q12w (with final dose at Week 36)
- Group 3: Ustekinumab 90 mg SC q8w (with final dose at Week 40)

Other Subject Populations

Subjects in the other populations will not be randomized, but rather will be assigned treatment as follows:

- Subjects in Clinical Response to Placebo Induction Dosing
  Subjects will continue to receive SC placebo throughout the maintenance study.

- Subjects Not in Clinical Response to Ustekinumab Induction Dosing
  Subjects will receive ustekinumab 90 mg SC at Week 0. If these subjects have achieved clinical response at Week 8, they will continue to receive ustekinumab 90 mg SC q8w through Week 40.
  If, by Week 8, these subjects have not achieved clinical response, they will be discontinued from further study agent administrations and will return for a final safety visit at Week 20 (ie, 20 weeks after the last administration of study agent).

- Subjects Not in Clinical Response to Placebo Induction Dosing
  Subjects will receive ustekinumab 130 mg via IV administration at Week 0. If these subjects have achieved clinical response at Week 8, they will initiate subcutaneous ustekinumab 90 mg SC at Week 8 and then q12w thereafter through Week 32.
  If, by Week 8, these subjects have not achieved clinical response, they will be discontinued from further study agent administrations and will return for a final safety visit at Week 20 (ie, 20 weeks after the last administration of study agent).

Treatment groups are depicted in the following figure:

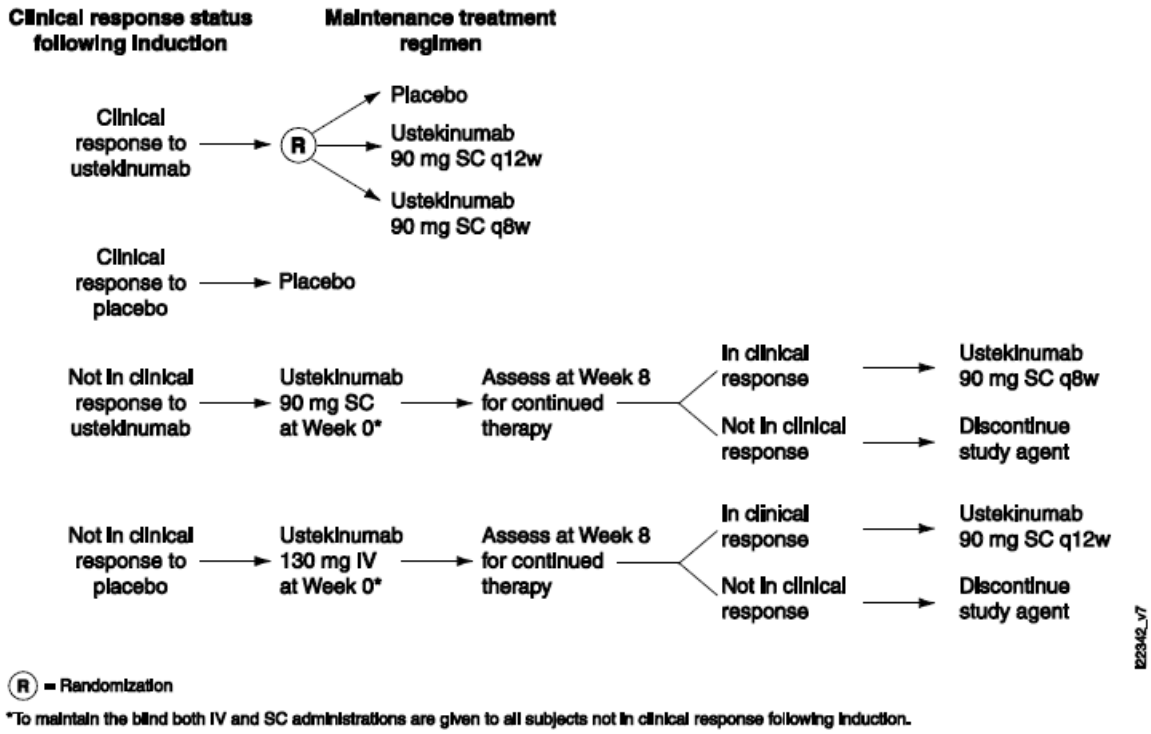


Figure 2 **Treatment Groups**

Dosage and Administration

All subjects were to receive an SC administration of study agent (either placebo or ustekinumab) every 4 weeks from Week 0 to Week 40 with the exception of Week 4.

Placebo administrations (both IV and SC) were given at dosing visits in which an active administration was not planned in order to maintain the blind, particularly with respect to SC regimen dosing interval (eg, a subject in the 90 mg ustekinumab q12w treatment group was to receive SC placebo at visits occurring 4 weeks and 8 weeks after receiving 90 mg ustekinumab).

All placebo IV induction subjects not in clinical response to induction dosing were to also receive an IV administration of ustekinumab at Week 0.

All ustekinumab IV induction non-responders received a placebo IV administration at Week 0 to maintain the induction study blind.

For subjects receiving an IV administration at Week 0, the study agent was to be administered over a period of not less than 1 hour. The infusion was to be completed within 5 hours of preparation.

The maintenance portion of the study continues to Week 44 (and the subsequent study extension will continue up to Week 272). The overall study design is shown in Figure 1:

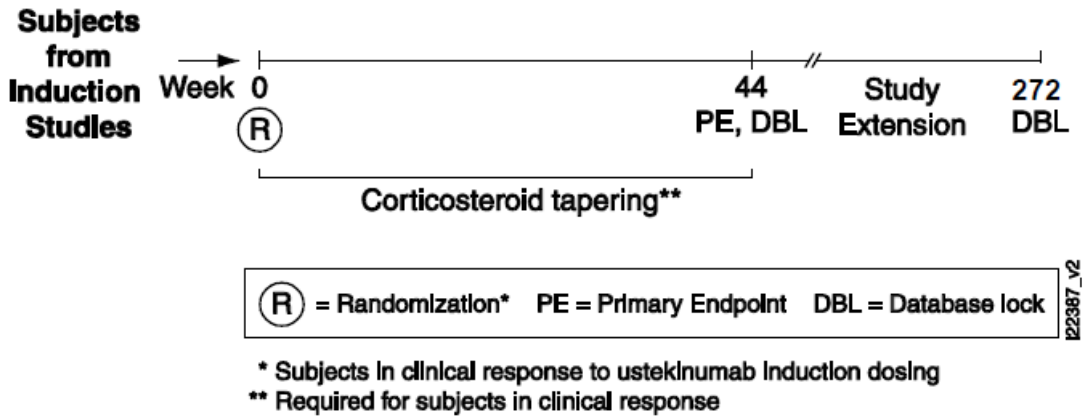


Figure 1 Study Design

Oral Corticosteroids Tapering

Subjects receiving corticosteroids at Week 0 who are in clinical response should initiate corticosteroid tapering at Week 0. This tapering is mandatory and should follow the below recommended schedule. Other subjects may also undergo tapering at the discretion of the investigator, and are encouraged to do so if demonstrating a clinical response at Week 4 or beyond.

If subjects experience a worsening in their disease activity while tapering corticosteroids, further dose decreases may be suspended, and/or their oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator. The oral corticosteroid dose, however, may not be increased above the baseline dose unless due to medical necessity. For subjects whose corticosteroid taper is interrupted on this basis, investigators are encouraged to resume tapering within 4 weeks. Tapering may exceed this schedule only if warranted by medical necessity (eg, subject experiencing corticosteroid-related side effects).

Recommended tapering schedule for oral corticosteroids (other than budesonide)

- Dose > 15 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until receiving 10 mg/day, then continue tapering at 2.5 mg/week until 0 mg/day.
- Dose 11 to 15 mg/day prednisone or equivalent: taper daily dose to 10 mg/day for 1 week, then continue at 2.5 mg/week until 0 mg/day.
- Dose ≤10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

Recommended tapering schedule for oral budesonide

Subjects receiving budesonide should have their daily dose tapered by 3 mg every 3 weeks until 0 mg/day.

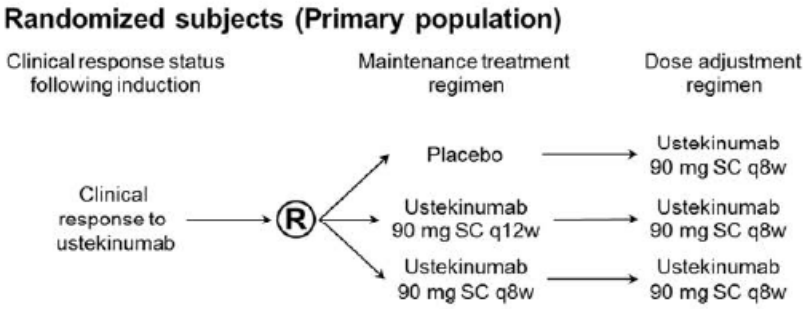
Dose Adjustment on Loss of Response (in clinical responders to induction)

Loss of response is defined as a CDAI score ≥ 220 points AND a ≥ 100 point increase from the Week 0 CDAI score (ie, Week 8 in induction study CNTO1275CRD3001 or CNTO1275CRD3002).

Subjects in the primary population induced into clinical response with ustekinumab in CNTO1275CRD3001 or CNTO1275CRD3002 who subsequently lose response at any scheduled visit will be eligible, beginning at Week 8, to receive ustekinumab dosing as follows:

- Group 1 (Placebo): Subjects will adjust to receive ustekinumab 90 mg SC q8w
- Group 2 (90 mg q12w): Subjects will adjust to receive ustekinumab 90 mg SC q8w
- Group 3 (90 mg q8w): Subjects will continue on ustekinumab 90 mg SC q8w

Dose adjustment is depicted in the following figure:



Subjects are only eligible for a single dose adjustment (the first time loss of response criteria is met). Subjects who have dose adjusted will be assessed 16 weeks after the visit where the loss of response criteria was met to determine if benefit was achieved from the dose adjustment.

Subjects who have not shown improvement in their Crohn's disease activity at that time (as assessed by the investigator) will be discontinued from study agent administration, and should return for a final safety visit approximately 20 weeks after the last study agent administration.

Subjects assessed by the investigator to be clinically improved will continue to receive the same adjusted dose, q8w in a blinded manner.

In order to allow sufficient time to assess benefit after dose adjustment, the Week 32 visit will be the final visit when loss of response criteria (and subsequent dose adjustment) can occur.

Objectives

Primary Objectives

- To evaluate clinical remission for the 2 subcutaneous (SC) maintenance regimens of ustekinumab in subjects with moderately to severely active Crohn's disease induced into clinical response with ustekinumab in the induction studies, CNTO1275CRD3001 and CNTO1275CRD3002.

- To evaluate the safety of 2 SC maintenance regimens of ustekinumab in subjects with moderately to severely active Crohn's Disease.

Secondary Objectives

- To evaluate the efficacy of ustekinumab in maintaining clinical response in subjects induced into clinical response.
- To evaluate the efficacy of ustekinumab in maintaining clinical remission in subjects induced into clinical remission.
- To evaluate the efficacy of ustekinumab in achieving corticosteroid free remission.
- To evaluate the pharmacokinetics, immunogenicity, and pharmacodynamics of ustekinumab therapy, including changes in CRP, fecal calprotectin, fecal lactoferrin, and other pharmacodynamic biomarkers.
- To evaluate the effect of ustekinumab on health related quality of life.

Outcomes/endpoints

Primary endpoint

- Clinical remission at Week 44 (defined as a CDAI score of < 150 points)

Major secondary endpoints in order of importance were:

1. Clinical response at Week 44.
2. Clinical remission at Week 44 among subjects in clinical remission to ustekinumab at Week 0.
3. Corticosteroid-free remission at Week 44.
4. Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF-antagonist therapy (ie, subjects from induction study CNTO1275CRD3001).

Clinical response was defined as a reduction from Week 0 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 in the CDAI score of ≥100 points. Subjects with a CDAI score of ≥220 to ≤248 points at Week 0 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 were considered to be in clinical response if a CDAI score of <150 is attained.

Efficacy was also evaluated by means of:

- Inflammatory Markers
  - ❖ C-reactive Protein
  - ❖ Fecal Lactoferrin and Calprotectin
- Patient-Reported Outcomes
  - ❖ Inflammatory Bowel Disease Questionnaire
  - ❖ 36-Item Short-form Health Survey
- Clinical assessment of:
  - ❖ Fistulas
  - ❖ Pyoderma Gangrenosum

- ❖ Mucosal Healing – by endoscopy at selected centres with video assessed at a central facility

Clinical safety was evaluated based on adverse events / clinical laboratory test results / physical examination / ECGs, as described.
Subjects also completed: the Work Limitations Questionnaire, a Productivity Visual Analog Scale and Time Lost from Work

Sample size

Assuming a 15% clinical remission rate at Week 44 in the placebo group and 35% in the 90 mg q8w ustekinumab group, 100 subjects per treatment group were predicted to yield power above 90%, at a significance level of 0.05 (2-sided).

The number of subjects enrolled in this study was dependent on the number of subjects entering from the induction studies, CRD3001 and CRD3002. The number of subjects in the primary analysis population was dependent on the number of subjects in clinical response to ustekinumab in the induction studies who consented to participate in the maintenance study. Assuming clinical response rates of 35% and 40% in the 2 ustekinumab dose groups in the CRD3001 study, and clinical response rates of 45% and 50% in the CRD3002 study, and an assumption of 10% drop out rate, approximately 322 responders (approximately 107 per treatment group) were predicted to enter into the maintenance study. Note that this calculation excludes the subjects who were randomized in the induction studies prior to them being placed on hold by the Sponsor in November 2011.

Randomisation

Primary Population

Subjects who were in clinical response to ustekinumab induction in either study CRD3001 or CRD3002 were randomly assigned to 1 of 3 treatment groups (placebo, ustekinumab 90 mg SC q12w, and ustekinumab 90 mg SC q8w) based on a computer-generated randomization schedule prepared before the study under the supervision of the Sponsor. Permuted block randomization with stratification factors of clinical remission at Week 0 (yes or no) and ustekinumab induction dose (130 mg or tiered dosing approximating 6 mg/kg ustekinumab) were used.

Other Subject Populations

Subjects in the other populations were not randomized (they were assigned treatments, as described).

Blinding (masking)

To maintain the study blind, the study agent container was to have a multilingual label containing the study name, medication number, and reference number. A tear-off label was designed to be separated from the study agent container and attached to the subject's source documents; the label was not to identify the study agent in the container. The medication number was to be entered in the case report form (CRF) when the study agent was dispensed. Study agents were packaged so as to be identical in appearance in order to maintain the study blind.

The Sponsor was blinded to treatment assignment until after the Week 44 database lock occurred. Treatment assignment blinding was maintained for investigative sites, site monitors and subjects participating in the study until the Week 44 analyses were completed.

Statistical methods

Analysis populations: Efficacy analyses were based on the primary analysis population (ie, subjects in clinical response to ustekinumab at Week 8 from 1 of the induction studies CNTO1275CRD3001 and CNTO1275CRD3002 excluding the subjects who were randomized prior to study restart). All subjects who received at least 1 dose of ustekinumab either in this study or in one of the induction studies, were included in the PK analyses. The safety analyses included all subjects who received study agent at Week 0.

The proportion of subjects in clinical remission at Week 44 was compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran Mantel Haenszel chi-square test, stratified by clinical remission status at Week 0 (yes or no), ustekinumab induction dose (130 mg or tiered dosing approximating ustekinumab 6 mg/kg), and the induction study (CNTO1275CRD3001 or CNTO1275CRD3002) at a significance level of 0.05. The study was considered positive if the 90 mg q8w ustekinumab group was significantly different from placebo.

The major secondary endpoints were compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran-Mantel-Haenszel chi square test, stratified by clinical remission status at Week 0 (yes or no), ustekinumab induction dose (130 mg or tiered dosing approximating ustekinumab 6 mg/kg), and the induction study (CNTO1275CRD3001 or CNTO1275CRD3002) at a significance level of 0.05.

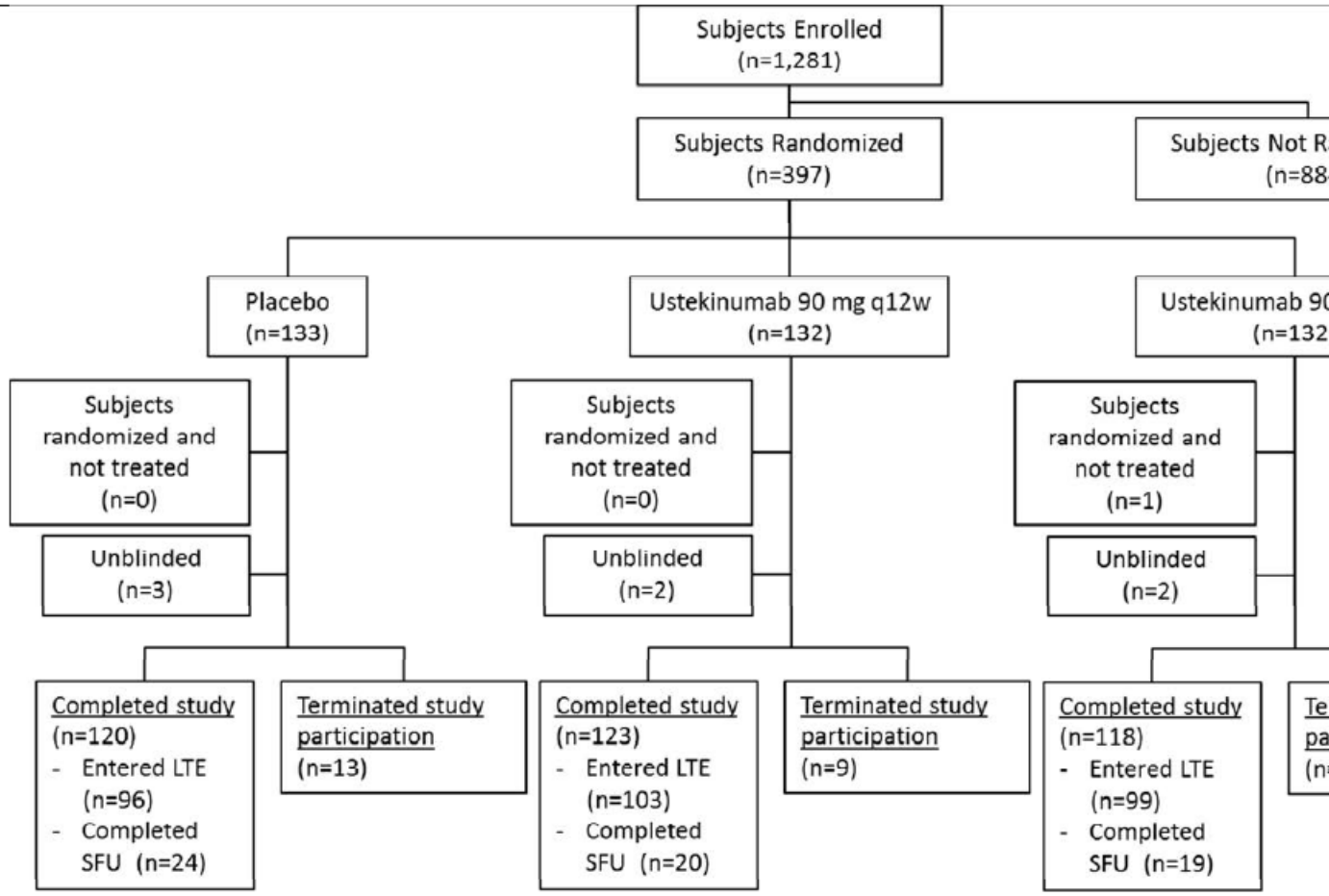
Global multiple testing procedures were prespecified to control the overall Type 1 error rate at the 0.05 level over the primary and major secondary endpoints in this study. All statistical testing was performed at the 2-sided 0.05 significance level. Nominal p-values are presented.

Safety analyses were assessed by summarizing the frequency and type of AEs and changes from baseline in clinical laboratory parameters for hematology and chemistry analyses. Safety summaries are provided for randomized subjects (ie, the primary population) to provide a balanced comparison across treatment groups, and for all treated subjects, including both randomized and nonrandomized subjects, to provide overall safety across the placebo and ustekinumab groups.

Results

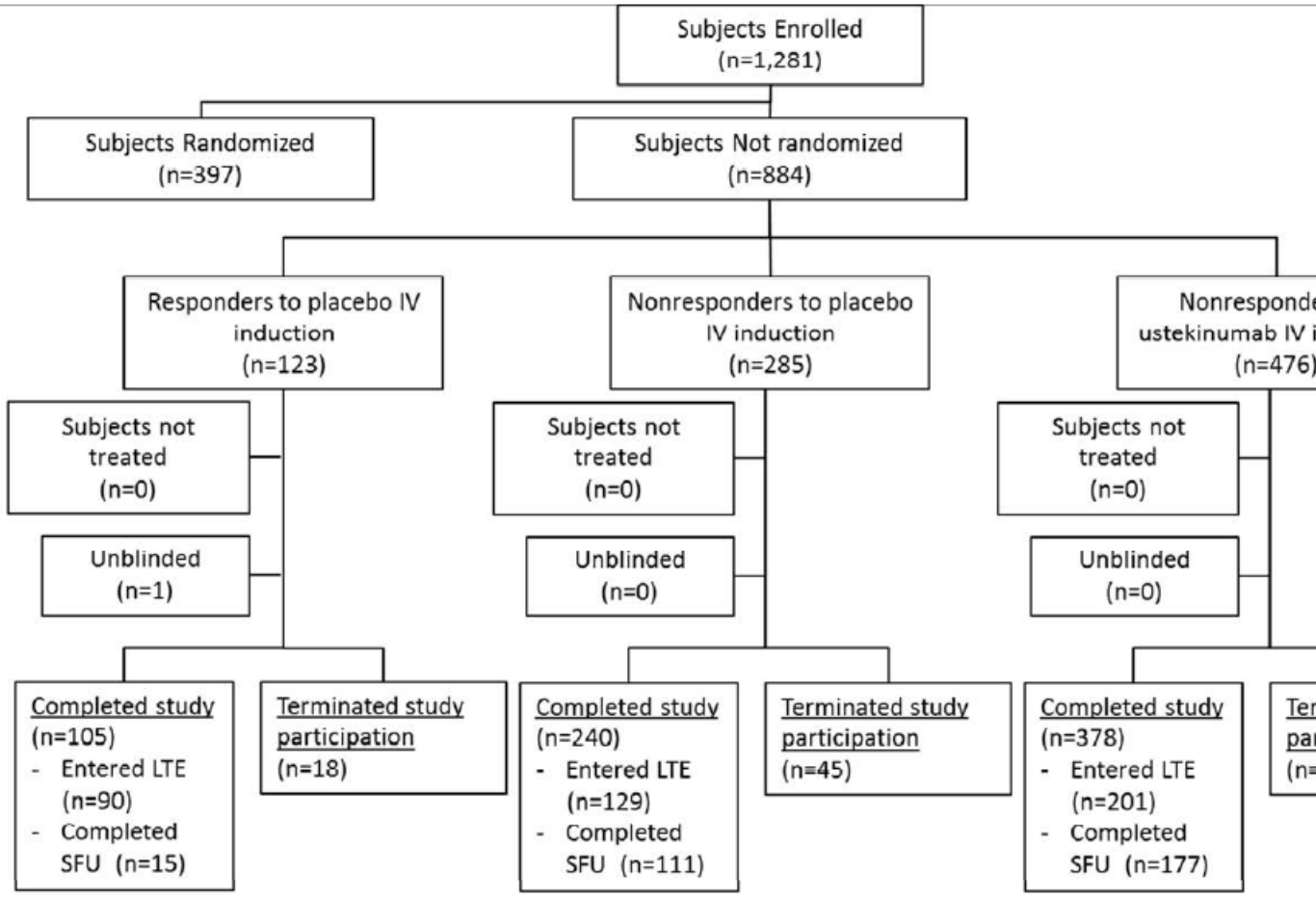
Participant flow

Figure 3: Subject disposition in Study CNTO1275CRD3003: Randomized subjects



LTE= long-term extension; SFU= safety follow-up

Figure 4: Subject disposition in Study CNTO1275CRD3003: Nonrandomized subjects



LTE= long-term extension; SFU= safety follow-up

Recruitment

Study start: 13th September 2011
Study completion: 10th June 2015
Study report: 9th November 2015

Conduct of the study

Protocol deviations varied in nature and were not considered to have any clinically relevant impact on data integrity or subject safety. There were carried out 3 amendments to the study all of them unlikely to affect study outcome / interpretation of results.

Baseline data

Study population; randomised patients only

A total of 397 patients were randomised in the study: 133 in the placebo group, 132 in the ustekinumab 90 mg 12 weekly group, and 132 in the ustekinumab 90 mg 8 weekly group. Of the randomised population 56.4% were female, 84.9% were Caucasian, the median age was 36.0 years and median weight 69.0 kg. Baseline demographic characteristics were generally similar across the treatment groups (Table 10).

The proportions of randomised patients who discontinued study agent were similar across treatment groups (23.3%, 22.0%, and 22.7% in the placebo, ustekinumab 12 weekly, and ustekinumab 8 weekly groups, respectively). The most common reasons for discontinuation were lack of efficacy or an adverse event. Among randomised patients, 9.8%, 6.8%, and 10.6% in the placebo, ustekinumab 12 weekly and ustekinumab 8 weekly groups, respectively, terminated study participation prior to Week 44. The most common reason for termination was withdrawal of consent.

Baseline disease characteristics were representative of a population of patients with moderate to severe Crohn's disease that was refractory to available therapies and were generally well balanced across the 3 treatment groups: median duration of disease at baseline, 7.57 years; median CDAI score, 311.0; median CRP concentration, 9.27 mg/L.

Of the randomised patients in this study, 44.8% were TNF antagonist refractory, 15.6% had received TNF antagonists and had not demonstrated failure or intolerance, and 39.5% had not received any TNF antagonist therapy prior to study participation. Additionally, 79.3% of patients were receiving 1 or more concomitant medications for Crohn's disease at baseline, and the proportions of patients receiving each class of Crohn's disease medication at baseline were similar across the 3 treatment groups. A total of 181 patients (45.6%) were receiving corticosteroids (including budesonide); 143 (36.0%) patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate).

Table 10 Baseline data by treatment group randomised patients; data are mean (s.d.)

	Placebo	**Ustekinumab 12 weekly**	**Ustekinumab 8 weekly**
N	133	132	132
Age (years)	39.5 (12.69)	38.6 (13.65)	37.9 (13.20)
Male/female (%)	44.4/55.6	43.9/56.1	42.4/57.6
Weight (kg)	72.31 (17.27)	69.99 (19.61)	70.61 (16.89)
Height (cms))	170.80 (9.92)	169.40 (10.35)	169.12 (10.12)
No. (%) in clinical remission	80 (60.2%)	80 (60.2%)	80 (60.2%)
CDIA score	143.5 (73.39)	141.8 (66.52)	130.6 (63.91)
IBDQ score	163.6 (32.04)	166.2 (32.81)	170.8 (29.02)

Non-randomised Patients:

A total of 884 patients were enrolled but not randomised: 123 placebo induction responders, 285 placebo induction non-responders, and 476 ustekinumab induction non-responders. Baseline demographic characteristics were generally similar to those noted for randomised patients.

A total of 455 (51.5%) non-randomised patients discontinued study agent. The most common reason for discontinuation of study agent was lack of efficacy.

Numbers analysed

Primary population**:** Efficacy analyses were based on the primary population. This included all randomised subjects. Subjects were only randomised if they were in clinical response to ustekinumab at Week 8 from one of the induction studies CRD3001 and CRD3002. Efficacy analyses were based on an intent-to-treat principle, i.e. the efficacy data for each subject was analysed according to the assigned treatment regardless of the actual treatment received.

Outcomes and estimation

Primary Efficacy Analysis

The primary endpoint was clinical remission at Week 44.

The proportions of subjects in the primary analysis population in clinical remission at Week 44 were 48.8% and 53.1% in the ustekinumab 90 mg q12w and q8w groups, respectively compared with 35.9% of subjects in the placebo group (Table 5):

Table 5: Number of subjects in clinical remission at Week 44; randomized subjects excluding those enrolled prior to study re-start

		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Week 44				
N	131	129	128	257
Subjects in clinical remission[b,c]	47 (35.9%)	63 (48.8%)	68 (53.1%)	131 (51.0%)
p-value		0.040	0.005	0.005

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission.

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The comparison between each of the 2 ustekinumab groups and the placebo group was statistically significant (p=0.040 and p=0.005 for the q12w and q8w groups, respectively, versus placebo). This study was considered to be a positive study because the ustekinumab 90 mg q8w group was significantly different from the placebo group.

The proportion of subjects in the primary analysis population who met treatment failure criteria prior to Week 44 was greater in the placebo group (45.0%) compared with the ustekinumab 90 mg q12w and q8w groups (36.4% and 28.9%, respectively):

TEFTF01: Number of subjects who met treatment failure criteria prior to Week 44; randomized subjects excluding those enrolled prior to study re-start

	placebo SC[a]	ustekinumab 90 mg SC q12w	ustekinumab 90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Subjects who met the treatment-failure criteria	59 (45.0%)	47 (36.4%)	37 (28.9%)	84 (32.7%)
Subjects who had specified changes in concomitant Crohn's disease medication	10 (7.6%)	16 (12.4%)	7 (5.5%)	23 (8.9%)
Subjects who discontinued study agent due to lack of efficacy or due to an adverse event indicated to be worsening Crohn's disease	20 (15.3%)	22 (17.1%)	17 (13.3%)	39 (15.2%)
Subjects who had a loss of clinical response	51 (38.9%)	29 (22.5%)	28 (21.9%)	57 (22.2%)
Subjects who had a Crohn's disease-related surgery as a result of lack of efficacy of study agent	5 (3.8%)	4 (3.1%)	2 (1.6%)	6 (2.3%)

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.

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The most common reason for meeting treatment failure criteria was loss of clinical response (38.9%, 22.5%, and 21.9% in the placebo, ustekinumab 90 mg q12w and q8w groups, respectively).

The proportion of subjects with missing data for the CDAI score at Week 44 (ie <4 of the 8 CDAI components available) was approximately 5% overall and the proportions across the 3 dose groups were 6.1%, 1.6%, and 7.8% in the placebo, ustekinumab 90 mg q12w and q8w dose groups, respectively.

Major Secondary Analyses

The major secondary efficacy analyses were evaluated using the primary analysis population.

Clinical Response at Week 44

The proportions of randomized subjects in clinical response at Week 44 were greater in the ustekinumab 90 mg q12w and q8w dose groups (58.1% and 59.4%, respectively) compared with the placebo group (44.3%; Table 6):

Table 6: Number of subjects in clinical response at Week 44; randomized subjects excluding those enrolled prior to study re-start

	placebo SC[a]	ustekinumab 90 mg SC q12w	ustekinumab 90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Week 44				
N	131	129	128	257
Subjects in clinical response [b,c]	58 (44.3%)	75 (58.1%)	76 (59.4%)	151 (58.8%)
p-value		0.033	0.018	0.009

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical response, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical response.

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The comparisons between both ustekinumab groups and placebo were significant (p=0.033 and p=0.018 for the q12w and q8w groups, respectively).

Clinical Remission at Week 44 among Subjects in Clinical Remission to Ustekinumab at Week 0

Approximately 60% of the subjects in the primary analysis population were in clinical remission at Week 0 of this maintenance study. Among those subjects, the proportions of subjects who maintained clinical remission (ie, were in clinical remission at both Week 0 and Week 44) was numerically greater in the ustekinumab 90 mg q12w dose group and significantly greater in the ustekinumab q8w group (56.4% and 66.7%, respectively) compared with the placebo group (45.6%; p = 0.189 and p = 0.007 for the q12w and q8w groups, respectively, versus placebo; Table 7):

Table 7: Number of subjects in clinical remission at Week 44; randomized subjects who were in clinical remission at Week 0, excluding those enrolled prior to study re-start

	placebo SC[a]	ustekinumab 90 mg SC q12w	ustekinumab 90 mg SC q8w	Combined
Analysis set: Randomized subjects who were in clinical remission at Week 0, excluding those enrolled prior to study re-start	79	78	78	156
Week 44				
N	79	78	78	156
Subjects in clinical remission[b,c]	36 (45.6%)	44 (56.4%)	52 (66.7%)	96 (61.5%)
p-value		0.189	0.007	0.019

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission.

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Corticosteroid-free Remission at Week 44

The proportions of subjects in clinical remission and not receiving concomitant corticosteroids at Week 44 were 42.6% and 46.9% in the ustekinumab 90 mg q12w and q8w dose groups, respectively, compared with 29.8% in the placebo group (p=0.035 and p=0.004 for the ustekinumab q12w and q8w groups, respectively, versus placebo; Table 8).

Table 8: Number of subjects in clinical remission at Week 44 and not receiving corticosteroids at Week 44; randomized subjects excluding those enrolled prior to study re-start

		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Week 44 N	131	129	128	257
Subjects in clinical remission at Week 44 and not receiving corticosteroids at Week 44[b,c,d]	39 (29.8%)	55 (42.6%)	60 (46.9%)	115 (44.7%)
p-value		0.035	0.004	0.004

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission.
[d] Subjects who had a missing value in corticosteroids use at designated analysis timepoint had their last value carried forward.

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While the nominal p-values for the comparisons of each of the ustekinumab groups with placebo were <0.05 for this endpoint, only the ustekinumab q8w regimen can be considered as significantly different from placebo within the global multiple testing procedure.

Clinical Remission at Week 44 in the Subset of Subjects Who Were Refractory or Intolerant to TNF Antagonist Therapy

Among subjects who were randomized in this maintenance study and refractory or intolerant to TNF antagonist therapy (ie, were ustekinumab responders at Week 8 of the induction study CRD3001), remission rates at Week 44 were numerically greater (38.6% and 41.1%) in the ustekinumab 90 mg q12w and q8w dose groups, respectively, compared with the placebo group (26.2%), though these differences were not statistically significant (Table 9):

Table 9: Number of subjects in clinical remission at Week 44; randomized subjects who were refractory or intolerant to TNF-antagonist therapy, excluding those enrolled prior to study re-start

	placebo SC[a]	ustekinumab 90 mg SC q12w	ustekinumab 90 mg SC q8w	Combined
Analysis set: Randomized subjects who were refractory or intolerant to TNF-antagonist therapy[d], excluding those enrolled prior to study re-start	61	57	56	113
Week 44				
N	61	57	56	113
Subjects in clinical remission[b,c]	16 (26.2%)	22 (38.6%)	23 (41.1%)	45 (39.8%)
p-value		0.140	0.102	0.070

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission.
[d] Subjects from CNTO1275CRD3001

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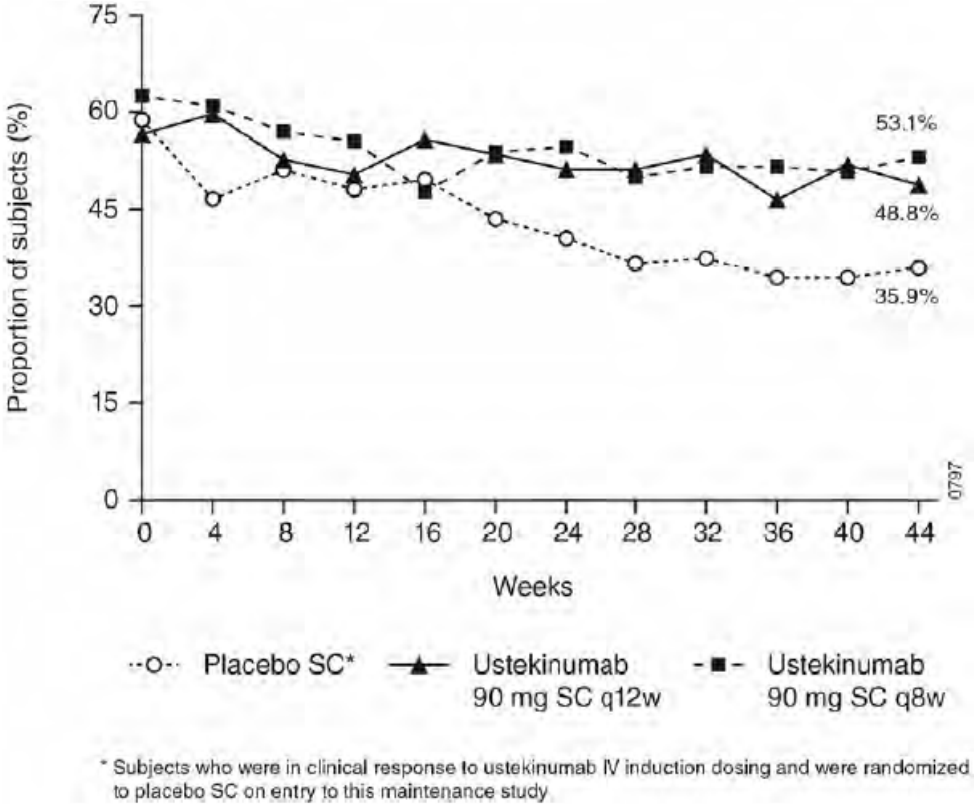
While the treatment effects were similar to those in the overall population, there was not sufficient power to detect a significant difference from placebo as only 44.8% of the subjects in the primary population of this study were in this subpopulation.

Clinical Efficacy over Time

The proportions of randomized subjects in clinical remission through Week 44 are presented in Figure 8:

Figure 8: Proportion of subjects in clinical remission at each visit through Week 44; randomized subjects excluding those enrolled prior to study restart



* Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry to this maintenance study.

IV=intravenous; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

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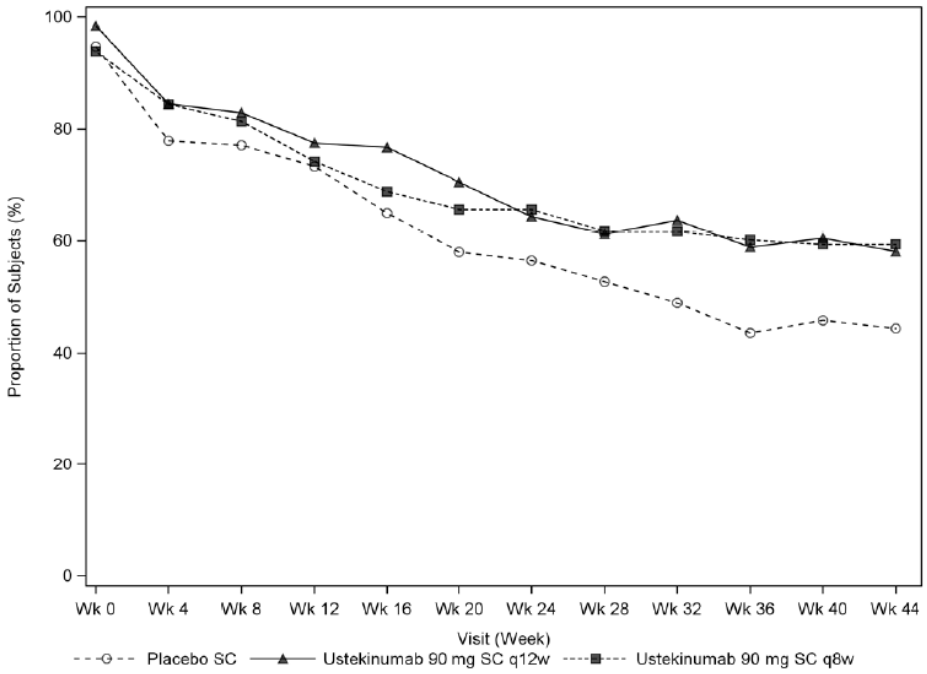
The proportions of subjects in clinical remission over time were generally similar for the ustekinumab 90 mg q12w and q8w groups, though remission rates were smallest for the ustekinumab q12w dose group at trough serum ustekinumab concentration visits (ie, Weeks 12, 24, and 36), and remission rates were generally more consistent for the ustekinumab q8w groups with the exception of Week 16.

The proportion of subjects in the placebo group who were in clinical remission decreased over time, with separation from the ustekinumab groups observed by Week 20.
When considering remission over time exclusively in the subset of responding subjects that were in remission upon entry to CRD3003 (ie remission in remitters), there was a decline over time to 66.7% at Week 44 in the q8w group (with a lower proportion of 56.4% on q12w). This decline was gradual and even slowed over time, and likely, the early loss of remission was impacted by mandatory steroid tapering.

In contrast, among the induction responders subsequently randomized to SC placebo, the rate of loss of response was more pronounced and these subjects continue to lose response at a greater rate than either SC dose. The one notable trend was that, as predicted by the half-life of ustekinumab, former recipients of the ~6 mg/kg dose tended to maintain efficacy until 16-20 weeks later (Weeks 8 to 12 of maintenance study), whereas loss of efficacy began to be apparent by the first maintenance visit at Week 4 in those having received the 130 mg dose.

The proportions of subjects in clinical response at each visit through Week 44 are presented in the following figure:

GEFCRES16: Proportion of subjects in clinical response at each visit through Week 44; randomized subjects excluding those enrolled prior to study re-start



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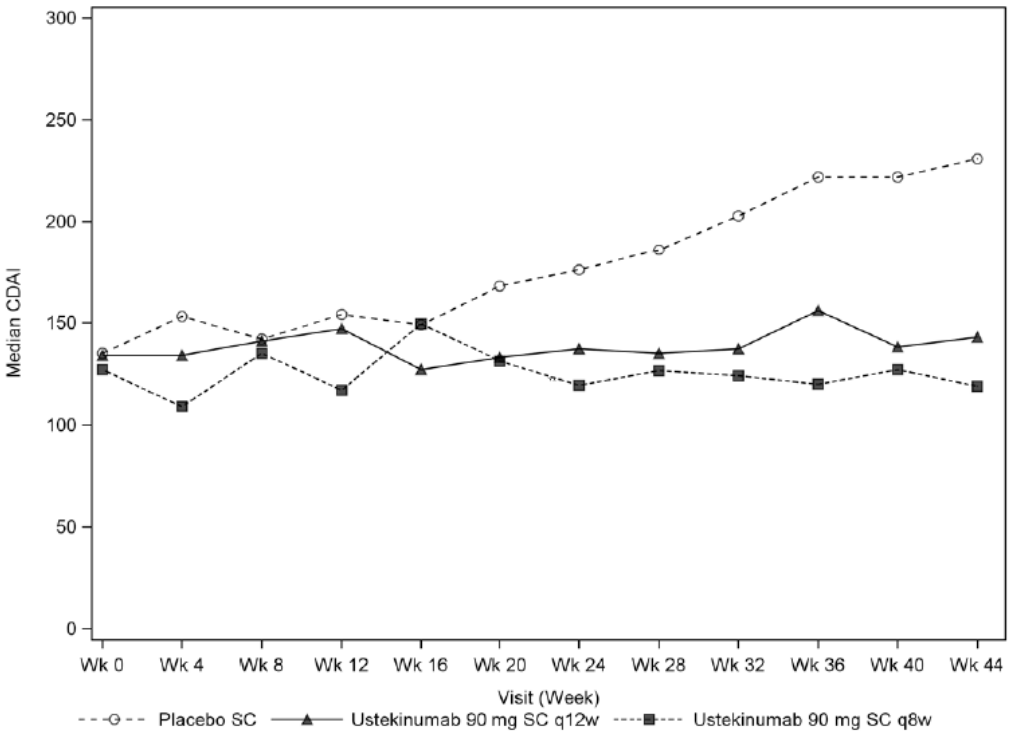
The proportions of subjects in clinical response in the ustekinumab groups were comparable and decrease from Week 0 of this study through Week 28 and plateau at approximately 60% through Week 44. The proportions of subjects in the placebo group in clinical response decreased over time with separation from the ustekinumab groups clearly observed by Week 20, and the greatest separation from treatment groups occurring after Week 28 and continuing through Week 44.

The median CDAI scores were generally consistent across the placebo, ustekinumab 90 mg q12w, and q8w groups at Week 0 of this maintenance study (135.0, 134.0, and 127.0, respectively). At visits from Week 4 to Week 44, median CDAI scores were maintained over time for subjects in the ustekinumab groups while scores increased over time for subjects in the placebo group, notably after Week 16, with clear separation from the ustekinumab groups by Week 20, as shown in the following figure:

GEFCDAI06: Line plot of median CDAI through Week 44; randomized subjects excluding those enrolled prior to study re-start



Clinical Efficacy With Dose Adjustment in Study CRD3003

Subjects who achieved clinical response with ustekinumab at Week 8 in CRD3001 or CRD3002 (ie, the primary population) and who subsequently had a loss of response (LOR) at a scheduled visit between Week 8 and Week 32 of this maintenance study were eligible for dose adjustment.

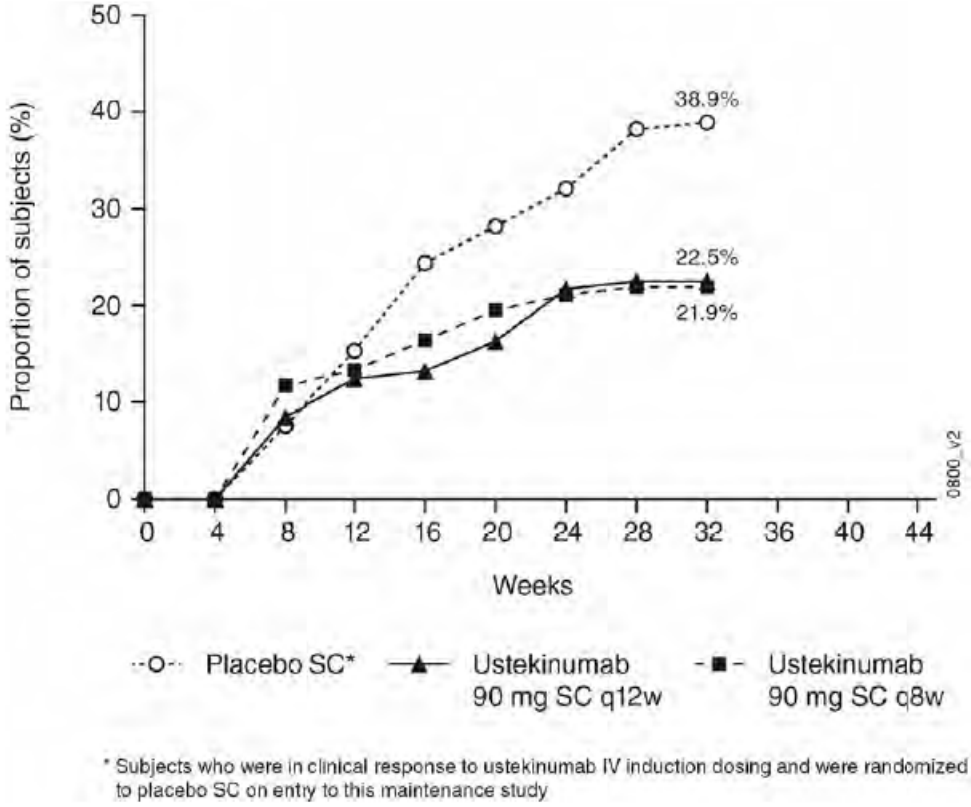
Eligible subjects randomized to ustekinumab q12w had a dose adjustment to a q8w regimen while subjects randomized to ustekinumab q8w meeting LOR criteria remained on the q8w regimen.

Subjects in the placebo group meeting LOR criteria had a dose adjustment to ustekinumab 90 mg q8w.

Subjects who had a dose adjustment were assessed 16 weeks after the visit where the loss of response criteria was met to determine if benefit was achieved from the dose adjustment.

The cumulative proportions of subjects meeting LOR criteria by treatment group are shown in Figure 12:

Figure 12: Cumulative proportion of subjects in the primary population meeting loss of response criteria for dose adjustment over time; randomized subjects CRD3003 excluding those enrolled prior to study restart



IV=intravenous; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.
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The proportions of subjects who met loss of response criteria in the placebo group increased over time to 38.9% at Week 32.

The cumulative proportions of subjects in the q8w and q12w groups who met loss of response criteria were similar over time, increasing through Week 24 and then remaining stable through Week 32 (the last allowable time for dose adjustment).

Clinical Efficacy in Subjects Who had a Dose Adjustment

LOR with dose adjustment (ustekinumab 90 mg q12w→ustekinumab 90 mg q8w):
29 subjects in the ustekinumab 90 mg q12w group had a dose adjustment to 90 mg q8w after meeting LOR criteria. When assessed 16 weeks after dose adjustment:

- 41.4% of these subjects were in clinical remission.
- 55.2% of these subjects had regained clinical response.
- The median change in CDAI score from time of dose adjustment was -141.0.

LOR without dose adjustment (ustekinumab 90 mg q8w→ustekinumab 90 mg q8w):

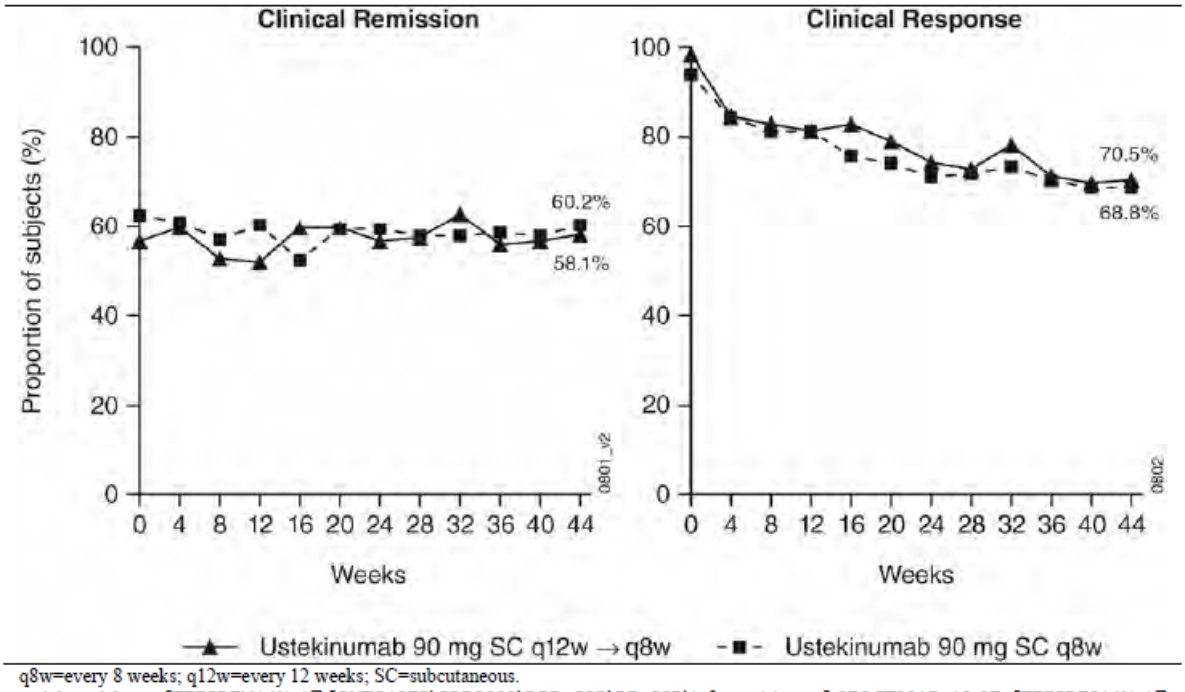
28 subjects in the ustekinumab 90 mg q8w group met LOR criteria for dose adjustment but continued to receive ustekinumab 90 mg q8w (per protocol). When assessed 16 weeks after meeting LOR criteria for dose adjustment:

- 32.1% of these subjects were in clinical remission.
- 46.4% of these subjects had regained clinical response.
- The median change in CDAI score from time of dose adjustment was -78.5.

Dose Adjustment as a Treatment Strategy

Having observed benefit within the group of subjects who had a dose adjustment from ustekinumab q12w to q8w, the data were alternatively evaluated through post-hoc analyses as a treatment strategy, an analytic approach that preserves the initial randomization.

Figure 13: Clinical remission and clinical response through Week 44 in CRD3003 by treatment strategy: ustekinumab 90 mg SC q12w→q8w and ustekinumab 90 mg SC q8w→ q8w



q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.
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Efficacy in Subjects Resuming Ustekinumab after Treatment Interruption

As part of the primary analysis population, subjects who were in response and were randomized to placebo were treated with ustekinumab 90 mg q8w upon meeting LOR criteria.

Resumption of ustekinumab treatment (placebo→ustekinumab 90 mg q8w): 51 subjects randomized to placebo had a dose adjustment to ustekinumab 90 mg q8w after meeting LOR criteria. At assessments 16 weeks after initiation of maintenance therapy:

- 39.2% of these subjects were in clinical remission.
- 70.6% of these subjects had regained clinical response.

— The median change in CDAI score from time of dose adjustment was -121.0.

These data indicate that in the subset of subjects who responded to the ustekinumab IV induction dose but delayed initiation of the SC maintenance therapy, benefit can be regained without the need for an additional IV induction dose. However, it should be noted that the number of subjects in this group was limited (51 subjects total) and the majority of patients (32 of 51 [63%]) had a dose adjustment within the first 16 weeks of the maintenance study.

Subjects randomized to placebo who initiated ustekinumab 90 mg SC q8w upon loss of response had higher rates of remission and response compared to the subjects in the placebo group in the pre-specified analysis.

Exposure to corticosteroids

The median average daily prednisone equivalent corticosteroid dose (excluding budesonide) at baseline was comparable between the ustekinumab dose groups (20.0 mg/day) and lower in the placebo groups (15.0 mg/day).

TSICM01C: Summary of concomitant medications for Crohn's disease at Week 0 of this maintenance study; randomized subjects

	placebo SC[a]	ustekinumab 90 mg SC q12w	ustekinumab 90 mg SC q8w	Combined	Total
Analysis set: Randomized subjects	133	132	132	264	397
Subjects with 1 or more concomitant medications	100 (75.2%)	106 (80.3%)	107 (81.1%)	213 (80.7%)	313 (78.8%)
Immunomodulatory drugs	45 (33.8%)	51 (38.6%)	43 (32.6%)	94 (35.6%)	139 (35.0%)
6-MP/AZA	38 (28.6%)	43 (32.6%)	30 (22.7%)	73 (27.7%)	111 (28.0%)
MTX	7 (5.3%)	8 (6.1%)	13 (9.8%)	21 (8.0%)	28 (7.1%)
Aminosalicylates	46 (34.6%)	47 (35.6%)	49 (37.1%)	96 (36.4%)	142 (35.8%)
Antibiotics	6 (4.5%)	7 (5.3%)	11 (8.3%)	18 (6.8%)	24 (6.0%)
Corticosteroids (including budesonide)	59 (44.4%)	58 (43.9%)	64 (48.5%)	122 (46.2%)	181 (45.6%)
Corticosteroids (P.Eq dose ; excluding budesonide) (mg/day)[b]					
N	51	46	51	97	148
Mean (SD)	18.2 (10.97)	17.9 (11.20)	18.5 (10.08)	18.2 (10.57)	18.2 (10.67)
Median	15.0	20.0	20.0	20.0	20.0
IQ range	(10.0; 25.0)	(5.0; 30.0)	(10.0; 25.0)	(10.0; 25.0)	(10.0; 25.0)
Range	(5; 50)	(3; 40)	(3; 40)	(3; 40)	(3; 50)
Budesonide dose (mg/day)					
N	8	12	12	24	32
Mean (SD)	7.9 (1.55)	8.0 (1.95)	8.5 (1.73)	8.3 (1.82)	8.2 (1.74)
Median	9.0	9.0	9.0	9.0	9.0
IQ range	(6.0; 9.0)	(7.5; 9.0)	(9.0; 9.0)	(9.0; 9.0)	(9.0; 9.0)
Range	(6; 9)	(3; 9)	(3; 9)	(3; 9)	(3; 9)

TSICM01C: Summary of concomitant medications for Crohn's disease at Week 0 of this maintenance study; randomized subjects

	placebo SC[a]	ustekinumab 90 mg SC q12w	ustekinumab 90 mg SC q8w	Combined	Total

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into the maintenance study.
[b] P.Eq: Predinisone equivalent

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Subjects receiving corticosteroids at Week 0 of the maintenance study who were in clinical response were to initiate mandatory corticosteroid tapering at Week 0.

The major secondary endpoint of corticosteroid-free remission at Week 44 in CRD3003 was achieved by a greater proportion of subjects in the ustekinumab 90 mg q12w and q8w groups (42.6% and 46.9%, respectively) compared with the placebo group (29.8%). While the nominal p-values for the comparisons of each of the ustekinumab groups with placebo were <0.05 for this endpoint, only the ustekinumab 90 mg q8w regimen can be considered as significantly different from placebo (p=0.004) within the global testing procedure.

Table 8: Number of subjects in clinical remission at Week 44 and not receiving corticosteroids at Week 44; randomized subjects excluding those enrolled prior to study re-start

		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Week 44 N	131	129	128	257
Subjects in clinical remission at Week 44 and not receiving corticosteroids at Week 44[b,c,d]	39 (29.8%)	55 (42.6%)	60 (46.9%)	115 (44.7%)
p-value		0.035	0.004	0.004

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission.
[d] Subjects who had a missing value in corticosteroids use at designated analysis timepoint had their last value carried forward.

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To confirm that results for steroid-free remission were reproducible, as well as reflected sufficient time as to be clinically meaningful steroid-free periods, the steroid-free remission analysis was also performed with the additional requirement of no steroid use for a minimum of 30 and also 90 days prior to the Week 44 primary maintenance endpoint.
The proportions of subjects in clinical remission at Week 44 who were not receiving concomitant corticosteroids for at least 30 or 90 days prior to Week 44 were similar. The proportions of subjects in the placebo group that were in remission and off steroids for 30 and 90 days (29.8% and 29%, respectively) were lower than in the 90 mg q12w (42.6% and 41.1%, respectively) as well as lower than the 90 mg q8w group (46.9% and 45.3%, respectively; p<0.05 for all comparisons vs placebo).

Consistent results were observed for steroid-free response, complimenting steroid-free remission at Week 44. The proportions of subjects in clinical response at Week 44 and not receiving corticosteroids were significantly greater in the ustekinumab 90 mg q12w and q8w groups (51.2% and 50.8%,

respectively) compared with subjects in the placebo group (36.6%; p=0.024 and p=0.026 for the q12w and q8w comparisons, respectively.

TEFCRES06: Number of subjects in clinical response at Week 44 and not receiving corticosteroids at Week 44; randomized subjects excluding those enrolled prior to study re-start

		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Week 44				
N	131	129	128	257
Subjects in clinical response at Week 44 and not receiving corticosteroids at Week 44 [b,c,d]	48 (36.6%)	66 (51.2%)	65 (50.8%)	131 (51.0%)
p-value		0.024	0.026	0.009

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical response, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical response.
[d] Subjects who had a missing value in corticosteroids use at designated analysis timepoint had their last value carried forward.

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Among the subgroup of subjects who were receiving corticosteroids at baseline (approximately 46%), a significantly greater proportion of these subjects in the combined ustekinumab group were able to discontinue corticosteroids and achieve clinical remission or clinical response at Week 44 (30.2% and 33.6%, respectively) compared with the placebo group (15.5% and 19.0%, respectively; p<0.05 for both vs placebo).
Though not independently statistically significant due to the smaller number of subjects in the subgroup on steroids at baseline, a higher proportion of subjects in both the 90 mg q12w and q8w groups achieved steroid-free remission and response at Week 44 compared with the placebo group.

Ancillary analyses

Subgroup analyses

In general, efficacy results for subgroups examining the primary endpoint of clinical remission at Week 44 were consistent with those of the overall study population. A single subgroup, weight at maintenance baseline >1st and ⩽2nd quartile had an OR<1 in the ustekinumab 90 mg q8w group compared with placebo. This was also observed for the q8w treatment group when using weight at induction baseline (OR=0.6, 95% CI: 0.2, 1.9).

Three ustekinumab 90 mg q12w treatment subgroups had an OR<1 compared with placebo. The first was the subgroup with weight at maintenance baseline >1st quartile and ⩽2nd quartile (OR=0.6, 95% CI: 0.2, 1.8), and the second was the subgroup with maintenance baseline CDAI <75 (OR=0.6, 95%

CI: 0.2, 2.3). The ustekinumab 90 mg q12w subgroup with CRP concentrations ⩽3 mg/L at induction baseline also had an OR<1 (OR=0.9, 95% CI: 0.3, 2.8).

When evaluated by Crohn's disease-related concomitant medication and prior CD medication subgroups at baseline of an induction study, the treatment effects of ustekinumab 90 mg q12w and q8w versus placebo were generally consistent with those of the primary analysis population with the exception of receiving both oral corticosteroids and 6-MP/AZA/MTX which had an OR<1 for both treatment groups compared with placebo (OR=0.5, 95% CI: 0.1, 2.9) for q12w group and OR=0.9, 95% CI: 0.2, 4.1) for q8w group.

Selected sub-groups within study CRD3003

Subjects entering the maintenance study CRD3003 from the induction study CRD3001 were required to have had documented failure with at least 1 TNF antagonist (ie, infliximab, adalimumab, or certolizumab pegol), either by having an inadequate initial response, by having a response followed by loss of response, or by being intolerant. Of the 397 randomized subjects in this study, 44.8% entered from CRD3001 and were TNF antagonist refractory.

Subjects entering the maintenance study CRD3003 from induction study CRD3002 were allowed to have previously received TNF antagonists, but they were not to have demonstrated inadequate response or intolerance to them. Of the 397 randomized subjects in this study, 55.2% entered from study CRD3002, 15.6% had received TNF antagonists and had not demonstrated failure or intolerance and 39.5% had not received any TNF antagonist therapy prior to study participation.

The proportions of subjects in clinical remission through Week 44 by induction study are presented in the following table:

TEFCREM13B: Number of subjects in clinical remission at each visit through Week 44 by induction study; randomized subjects excluding those enrolled prior to study re-start

	CNTO1275CRD3001				CNTO1275CRD3002			
		ustekinumab				ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	61	57	56	113	70	72	72	144
Week 0								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [d]	27 (44.3%)	27 (47.4%)	34 (60.7%)	61 (54.0%)	50 (71.4%)	46 (63.9%)	46 (63.9%)	92 (63.9%)
Week 4								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	21 (34.4%)	31 (54.4%)	30 (53.6%)	61 (54.0%)	40 (57.1%)	46 (63.9%)	48 (66.7%)	94 (65.3%)
p-value		0.012	0.039	0.008		0.297	0.096	0.115
Week 8								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	21 (34.4%)	26 (45.6%)	25 (44.6%)	51 (45.1%)	46 (65.7%)	42 (58.3%)	48 (66.7%)	90 (62.5%)
p-value		0.204	0.315	0.182		0.346	0.728	0.754
Week 12								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	20 (32.8%)	21 (36.8%)	29 (51.8%)	50 (44.2%)	43 (61.4%)	44 (61.1%)	42 (58.3%)	86 (59.7%)
p-value		0.714	0.045	0.157		0.991	0.869	0.933
Week 16								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	21 (34.4%)	27 (47.4%)	21 (37.5%)	48 (42.5%)	44 (62.9%)	45 (62.5%)	40 (55.6%)	85 (59.0%)
p-value		0.115	0.915	0.337		0.996	0.434	0.655
Week 20								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	19 (31.1%)	24 (42.1%)	22 (39.3%)	46 (40.7%)	38 (54.3%)	45 (62.5%)	47 (65.3%)	92 (63.9%)

TEFCREM13B: Number of subjects in clinical remission at each visit through Week 44 by induction study; randomized subjects excluding those enrolled prior to study re-start

	CNTO1275CRD3001				CNTO1275CRD3002			
		ustekinumab				ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
p-value		0.197	0.435	0.229		0.286	0.100	0.121
Week 24								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	18 (29.5%)	21 (36.8%)	22 (39.3%)	43 (38.1%)	35 (50.0%)	45 (62.5%)	48 (66.7%)	93 (64.6%)
p-value		0.380	0.317	0.270		0.122	0.012	0.022
Week 28								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	18 (29.5%)	22 (38.6%)	21 (37.5%)	43 (38.1%)	30 (42.9%)	44 (61.1%)	43 (59.7%)	87 (60.4%)
p-value		0.294	0.428	0.267		0.032	0.020	0.011
Week 32								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	15 (24.6%)	24 (42.1%)	22 (39.3%)	46 (40.7%)	34 (48.6%)	45 (62.5%)	44 (61.1%)	89 (61.8%)
p-value		0.032	0.109	0.031		0.091	0.081	0.049
Week 36								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	16 (26.2%)	19 (33.3%)	23 (41.1%)	42 (37.2%)	29 (41.4%)	41 (56.9%)	43 (59.7%)	84 (58.3%)
p-value		0.479	0.104	0.163		0.068	0.021	0.018
Week 40								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	15 (24.6%)	24 (42.1%)	22 (39.3%)	46 (40.7%)	30 (42.9%)	43 (59.7%)	43 (59.7%)	86 (59.7%)
p-value		0.053	0.106	0.038		0.049	0.031	0.017
Week 44								
N	61	57	56	113	70	72	72	144
Subjects in clinical remission [b,c]	16 (26.2%)	22 (38.6%)	23 (41.1%)	45 (39.8%)	31 (44.3%)	41 (56.9%)	45 (62.5%)	86 (59.7%)
p-value		0.140	0.102	0.070		0.146	0.020	0.029

At Week 44, the proportions of subjects in clinical remission were numerically greater for both ustekinumab treatment groups compared with placebo regardless of induction study and reached statistical significance for the ustekinumab 90 mg q8w group (p=0.020) in study CRD3002.

The proportions of subjects from study CRD3002 who were in clinical remission were greater than the proportions of subjects from study CRD3001 who were in clinical remission at all visits through Week 44.

For subjects from study CRD3002 who were TNF antagonist therapy naïve (n=156 subjects), the proportions of subjects in clinical remission at Week 44 were numerically greater in the ustekinumab 90 mg q12w group (56.6%) and significantly greater in the ustekinumab q8w group (65.4%) compared with the placebo group (49.0%; p=0.512 and p=0.041 for the ustekinumab 90 mg q12w and q8w groups, respectively, as shown in the following table:

TEFCREM13A: Number of subjects in clinical remission at each visit through Week 44; randomized subjects who were TNF naïve, excluding those enrolled prior to study re-start

		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects who were TNF naïve, excluding those enrolled prior to study re-start	51	53	52	105
Week 0				
N	51	53	52	105
Subjects in clinical remission [d]	40 (78.4%)	35 (66.0%)	33 (63.5%)	68 (64.8%)
Week 4				
N	51	53	52	105
Subjects in clinical remission [b,c]	32 (62.7%)	33 (62.3%)	34 (65.4%)	67 (63.8%)
p-value		0.717	0.207	0.370
Week 8				
N	51	53	52	105
Subjects in clinical remission [b,c]	37 (72.5%)	31 (58.5%)	35 (67.3%)	66 (62.9%)
p-value		0.229	0.938	0.535
Week 12				
N	51	53	52	105
Subjects in clinical remission [b,c]	33 (64.7%)	35 (66.0%)	32 (61.5%)	67 (63.8%)
p-value		0.630	0.674	0.649
Week 16				
N	51	53	52	105
Subjects in clinical remission [b,c]	35 (68.6%)	32 (60.4%)	29 (55.8%)	61 (58.1%)
p-value		0.524	0.406	0.362
Week 20				
N	51	53	52	105
Subjects in clinical remission [b,c]	30 (58.8%)	31 (58.5%)	35 (67.3%)	66 (62.9%)
p-value		0.906	0.119	0.368
Week 24				

TEFCREMI13A: Number of subjects in clinical remission at each visit through Week 44; randomized subjects who were TNF naïve, excluding those enrolled prior to study re-start

		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
N	51	53	52	105
Subjects in clinical remission [b,c]	30 (58.8%)	33 (62.3%)	34 (65.4%)	67 (63.8%)
p-value		0.735	0.172	0.353
Week 28				
N	51	53	52	105
Subjects in clinical remission [b,c]	25 (49.0%)	33 (62.3%)	32 (61.5%)	65 (61.9%)
p-value		0.208	0.065	0.073
Week 32				
N	51	53	52	105
Subjects in clinical remission [b,c]	28 (54.9%)	33 (62.3%)	31 (59.6%)	64 (61.0%)
p-value		0.467	0.345	0.360
Week 36				
N	51	53	52	105
Subjects in clinical remission [b,c]	22 (43.1%)	28 (52.8%)	32 (61.5%)	60 (57.1%)
p-value		0.336	0.026	0.072
Week 40				
N	51	53	52	105
Subjects in clinical remission [b,c]	23 (45.1%)	30 (56.6%)	33 (63.5%)	63 (60.0%)
p-value		0.266	0.025	0.053
Week 44				
N	51	53	52	105
Subjects in clinical remission [b,c]	25 (49.0%)	30 (56.6%)	34 (65.4%)	64 (61.0%)
p-value		0.512	0.041	0.124

A significantly greater proportion of subjects in the q12w and q8w groups were in sustained clinical remission (ie remission at Weeks 36, 40, and 44; 40.3% and 46.1%, respectively) compared with placebo (26.0%; p=0.023 and p<0.001, respectively).

Efficacy Analyses in Non-randomized Subjects

No statistical testing was performed. Corticosteroid tapering was not required in this population.
Results are summarised in the following tables:
Subjects in clinical response are summarised in the following table:

TEFCRES12: Number of subjects in clinical response at Week 44; non-randomized subjects excluding those enrolled prior to study re-start and excluding site 1127

	Responders to placebo IV induction dosing	Non-responders to IV induction dosing	
	placebo SC[a]	Non-responders to placebo IV induction dosing and received ustekinumab in maintenance[b]	Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance[c]
Analysis set: Non-randomized subjects excluding those enrolled prior to study re-start and excluding site 1127	120	279	467
Week 8			
N	120	279	467
Subjects in clinical response [d,e]	89 (74.2%)	148 (53.0%)	236 (50.5%)
Number of subjects who continued dosing at Week 8	118	159	251
Week 12			
N	118	159	251
Subjects in clinical response [d,e]	86 (72.9%)	120 (75.5%)	191 (76.1%)
Week 16			
N	118	159	251
Subjects in clinical response [d,e]	78 (66.1%)	114 (71.7%)	184 (73.3%)
Week 20			
N	118	159	251
Subjects in clinical response [d,e]	78 (66.1%)	108 (67.9%)	175 (69.7%)
Week 24			
N	118	159	251
Subjects in clinical response [d,e]	73 (61.9%)	114 (71.7%)	173 (68.9%)
Week 28			
N	118	159	251
Subjects in clinical response [d,e]	68 (57.6%)	115 (72.3%)	172 (68.5%)
Week 32			
N	118	159	251
Subjects in clinical response [d,e]	67 (56.8%)	102 (64.2%)	172 (68.5%)
Week 36			
N	118	159	251
Subjects in clinical response [d,e]	69 (58.5%)	101 (63.5%)	165 (65.7%)
Week 40			
N	118	159	251
Subjects in clinical response [d,e]	65 (55.1%)	106 (66.7%)	169 (67.3%)

TEFCRES12: Number of subjects in clinical response at Week 44; non-randomized subjects excluding those enrolled prior to study re-start and excluding site 1127

	Responders to placebo IV induction dosing	Non-responders to IV induction dosing	
	placebo SC[a]	Non-responders to placebo IV induction dosing and received ustekinumab in maintenance[b]	Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance[c]
Week 44			
N	118	159	251
Subjects in clinical response[d,e]	66 (55.9%)	106 (66.7%)	171 (68.1%)

[a] Subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into this maintenance study.
[b] Subjects who received ustekinumab 130 mg IV at Week 0. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q12w.
[c] Subjects who received ustekinumab 90 mg SC at Week 0. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q8w.
[d] Subjects who had a prohibited Crohn's disease-related surgery, discontinue due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease, or had prohibited concomitant medication changes prior to the designated analysis timepoint are considered not to be in clinical response, regardless of their CDAI score.
[e] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical response.

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Ustekinumab induction non-responders (n=467): Subjects in this group received ustekinumab 90 mg SC at Week 0. At Week 8, 50.5% were in clinical response.

Of these subjects, 251 continued dosing at Week 8 with ustekinumab 90 mg SC q8w. At Week 44, 68.1% of these delayed responders were in clinical response.

Placebo induction non-responders (n=279): Subjects in this group received ustekinumab 130 mg IV at Week 0. At Week 8, 53.0% were in clinical response.

Of these subjects, 159 continued dosing at Week 8 with ustekinumab 90 mg SC q12w. At Week 44, 66.7% of these subsequent induction responders were in clinical response.

Placebo induction responders (n=120): Subjects in this group received placebo SC at Week 0. At Week 8, 74.2% of placebo induction responders were in clinical response.

Of these subjects, 118 continued dosing with placebo. At Week 44, 55.9% were in clinical response.

Subjects in remission are summarised in the following table:

TEFCREM12: Number of subjects in clinical remission at each visit from Week 8 to Week 44; non-randomized subjects excluding those enrolled prior to study re-start and excluding site 1127

	Responders to placebo IV induction dosing	Non-responders to IV induction dosing	
	placebo SC[a]	Non-responders to placebo IV induction dosing and received ustekinumab in maintenance[b]	Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance[c]
Analysis set: Non-randomized subjects excluding those enrolled prior to study re-start and excluding site 1127	120	279	467
Week 8			
N	120	279	467
Subjects in clinical remission [d,e]	64 (53.3%)	80 (28.7%)	135 (28.9%)
Number of subjects who continued dosing at Week 8	118	159	251
Week 12			
N	118	159	251
Subjects in clinical remission [d,e]	61 (51.7%)	75 (47.2%)	120 (47.8%)
Week 16			
N	118	159	251
Subjects in clinical remission [d,e]	63 (53.4%)	70 (44.0%)	120 (47.8%)
Week 20			
N	118	159	251
Subjects in clinical remission [d,e]	63 (53.4%)	69 (43.4%)	114 (45.4%)
Week 24			
N	118	159	251
Subjects in clinical remission [d,e]	57 (48.3%)	77 (48.4%)	122 (48.6%)
Week 28			
N	118	159	251
Subjects in clinical remission [d,e]	56 (47.5%)	79 (49.7%)	128 (51.0%)
Week 32			
N	118	159	251
Subjects in clinical remission [d,e]	57 (48.3%)	71 (44.7%)	125 (49.8%)
Week 36			
N	118	159	251
Subjects in clinical remission [d,e]	61 (51.7%)	72 (45.3%)	128 (51.0%)
Week 40			
N	118	159	251

TEFCREM12: Number of subjects in clinical remission at each visit from Week 8 to Week 44; non-randomized subjects excluding those enrolled prior to study re-start and excluding site 1127

	Responders to placebo IV induction dosing	Non-responders to IV induction dosing	
	placebo SC[a]	Non-responders to placebo IV induction dosing and received ustekinumab in maintenance[b]	Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance[c]
Subjects in clinical remission [d,e]	55 (46.6%)	78 (49.1%)	131 (52.2%)
Week 44			
N	118	159	251
Subjects in clinical remission [d,e]	56 (47.5%)	79 (49.7%)	126 (50.2%)

[a] Subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into this maintenance study.
[b] Subjects who received ustekinumab 130 mg IV at Week 0. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q12w.
[c] Subjects who received ustekinumab 90 mg SC at Week 0. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q8w.
[d] Subjects who had a prohibited Crohn's disease-related surgery, discontinue due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease, or had prohibited concomitant medication changes prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score.
[e] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission.

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Ustekinumab induction non-responders (n=467): Subjects in this group received ustekinumab 90 mg SC at Week 0. At Week 8, 28.9% were in clinical remission.
Of these subjects, 251 continued dosing at Week 8 with ustekinumab 90 mg SC q8w. At Week 44, 50.2% were in clinical remission.

Placebo induction non-responders (n=279): Subjects in this group received ustekinumab 130 mg IV at Week 0. At Week 8:, 28.7% were in clinical remission.
Of these subjects, 159 continued dosing at Week 8 with ustekinumab 90 mg SC q12w. At Week 44, 49.7% were in clinical remission.

Placebo induction responders (n=120): Subjects in this group received placebo SC at Week 0. At Week 8, 53.3% were in clinical remission.
Of these subjects, 118 continued dosing with placebo. At Week 44, 47.5% were in clinical remission.

Summary of main study

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

Table E3. Summary of efficacy for trial CRD3003

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease				
Study identifier	CRD3003			
Design	Randomised, double-blind, placebo-controlled multicentre study in patients achieving a response to ustekinumab in CRD3001 or CRD3002.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		44 weeks not applicable 228 weeks	
Hypothesis	Superiority			
Treatments groups	Ustekinumab 90mg q12w		SC administration of ustekinumab or placebo every 4 weeks; randomized n=129	
	Ustekinumab 90mg q8w		SC administration of ustekinumab or placebo every 4 weeks; randomized n=128	
	Placebo		SC administration of placebo every 4 weeks; randomized n=131	
Endpoints and definitions	Primary endpoint	Clinical Remission at week 44	CDAI score <150 at week 44	
	Major Secondary endpoint	Clinical Response at week 44	Reduction from baseline of induction study (CRD3001 or CRD3002) in the CDAI score of ≥100 points or to <150 at week 44	
	Major Secondary endpoint	Clinical Remission at week 44 amongst subjects in clinical remission at week 0	CDAI score <150 at week 44 at week 0 and week 44	
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat – all patients randomized after study re-start. Only patients responding to ustekinumab in study CRD3001 or CRD3002 were randomized.			
Descriptive statistics and estimate variability	Treatment group	Ustekinumab 90mg q12w	Ustekinumab 90mg q8w	Placebo
	Number of subjects	129	128	131
	Clinical remission at week 44	63 (48.8%)	68 (53.1%)	47 (35.9%)

Effect estimate per comparison		Comparison groups	Ustekinumab 90mg q12w vs. placebo	
		P-value	p=0.040	
		Comparison groups	Ustekinumab 90mg q8w vs. placebo	
		P-value	p=0.005	
Analysis description	**Major Secondary Endpoint**			
Analysis population and time point description	Intent to treat – all patients randomized after study re-start. Only patients responding to ustekinumab in study CRD3001 or CRD3002 were randomized.			
Descriptive statistics and estimate variability	Treatment group	Ustekinumab 90mg q12w	Ustekinumab 90mg q8w	Placebo
	Number of subjects	129	128	131
	Clinical response at week 44	75 (58.1%)	76 (59.4%)	58 (44.3%)
		Comparison groups	Ustekinumab 90mg q12w vs. placebo	
		P-value	p=0.033	
		Comparison groups	Ustekinumab 90mg q8w vs. placebo	
		P-value	p=0.018	
Analysis description	**Major Secondary Endpoint**			
Analysis population and time point description	All patients randomized after study re-start who were in clinical remission at week 0.			
Descriptive statistics and estimate variability	Treatment group	Ustekinumab 90mg q12w	Ustekinumab 90mg q8w	Placebo
	Number of subjects	78	78	79
	Clinical remission at week 44	44 (56.4%)	52 (66.7%)	36 (45.6%)
		Comparison groups	Ustekinumab 90mg q12w vs. placebo	
		P-value	p=0.189	
		Comparison groups	Ustekinumab 90mg q8w vs. placebo	
		P-value	p=0.007	

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

Comparisons of results across studies use results of the Phase 3 induction studies which were the only studies that evaluated the same dosing regimens. With the exception of previous TNF antagonist

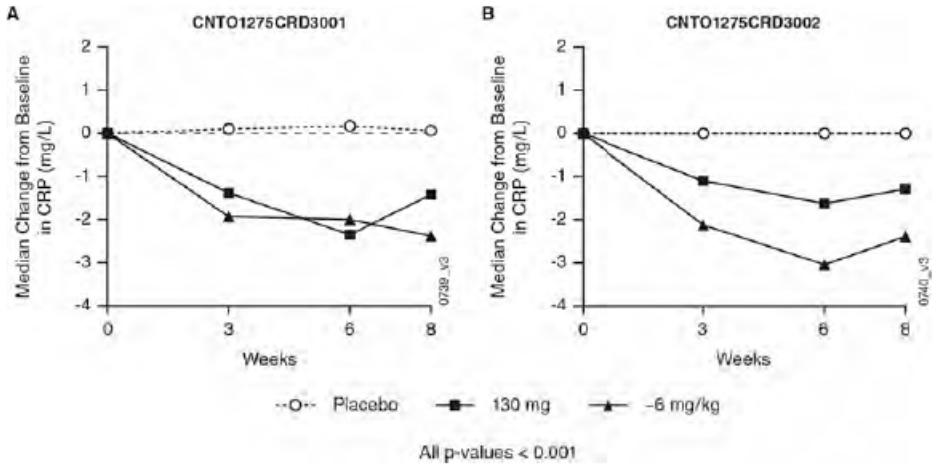
experience, these studies recruited similar subject populations and the studies were identical in design. The results across CRD3001 and CRD3002 were generally consistent in terms of the onset of efficacy and efficacy over time through Week 8.

C-reactive protein

Blood samples were taken to assay for high-sensitivity C-reactive protein. CRP was assayed using a validated, high-sensitivity CRP assay.

Greater median reductions from baseline in CRP concentration were observed at Weeks 3, 6, and 8 in both ustekinumab dose groups compared with placebo in both induction studies, as shown in figure below:

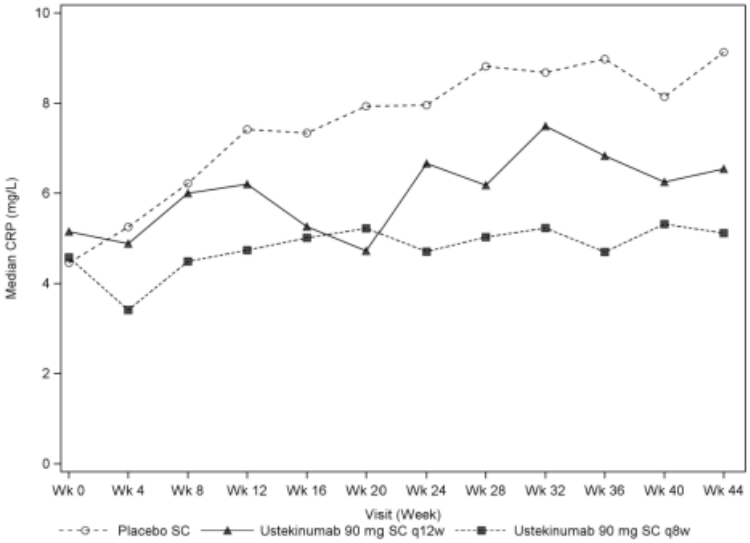
Figure 8: Change in CRP concentration through Week 8; randomized subjects in CRD3001 and CRD3002



Excludes subjects randomized before study restart and Site 1127. *Adapted from:* TEFCRP02 [CNTO1275\CRD3001\DBR_W8_W20\RE_W8_W20 and CNTO1275\CRD3002\DBR_W20\RE_W20]

Reduction in median CRP attained with study drug versus placebo was maintained at Week 44 in stdy 3003 in both ustekinumab dose groups compared with the placebo group, as shown in the figure below:

Figure 9: Median CRP through Week 44; randomized subjects in CNTO1275CRD3003



Excludes subjects randomized before study restart and Site 1127. *Adapted from:* GEFCRP03 [CNTO1275\CRD3003\DBR_CSR\RE_CSR]

Fecal Calprotectin

Assays for fecal content of calprotectin were performed using a validated method.

In both induction studies, at Week 6, there was a significantly greater reduction in fecal calprotectin concentration in both the ~6 mg/kg and 130 mg ustekinumab groups compared with the placebo group:

Study 3001

TEFFECL03: Summary of Change from Baseline in Fecal Calprotectin Concentration (milligrams/kg) at Week 6; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start

	Placebo	130 mg	Ustekinumab 6 mg/kg[a]	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494
Baseline				
N	237	238	239	477
Mean (SD)	1133.60 (2108.979)	808.01 (1344.161)	963.03 (1364.250)	885.68 (1355.064)
Median	515.78	399.90	530.15	430.28
IQ range	(157.43; 1100.25)	(138.26; 990.08)	(130.76; 1297.90)	(136.17; 1146.60)
Range	(11.9; 16578.8)	(11.9; 14273.0)	(11.9; 10760.0)	(11.9; 14273.0)
Change from baseline				
Week 6[b,c]				
N	237	238	239	477
Mean (SD)	-50.87 (2242.881)	-174.48 (1180.096)	-239.13 (1242.714)	-206.87 (1211.034)
Median	0.00	-38.57	-41.25	-39.01
IQ range	(-124.80; 188.23)	(-280.23; 31.21)	(-382.87; 18.24)	(-320.03; 22.73)
Range	(-15992.0; 18637.4)	(-13347.4; 5203.9)	(-6127.3; 9871.0)	(-13347.4; 9871.0)
p-value		< 0.001	< 0.001	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Subjects who prior to Week 6 had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes had their baseline value carried forward.
[c] Subjects who had insufficient data at Week 6 had their last value carried forward.

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Study 3002:

TEFFECL03: Summary of Change from Baseline in Fecal Calprotectin Concentration (milligrams/kg) at Week 6; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127

	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/kg[a]	Ustekinumab Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start and excluding site 1127	209	209	209	418
Baseline				
N	204	205	203	408
Mean (SD)	665.19 (923.740)	784.66 (1025.130)	784.20 (1080.701)	784.43 (1051.851)
Median	415.54	519.63	523.23	521.08
IQ range	(116.38; 720.62)	(141.14; 941.80)	(179.59; 756.80)	(160.15; 833.58)
Range	(11.9; 6849.0)	(11.9; 6444.0)	(11.9; 8558.3)	(11.9; 8558.3)
Change from baseline Week 6[b,c]				
N	204	205	203	408
Mean (SD)	19.43 (893.981)	-187.70 (1211.066)	-312.69 (1110.046)	-249.89 (1162.161)
Median	0.00	-55.03	-106.32	-73.16
IQ range	(-85.06; 175.72)	(-282.50; 13.70)	(-471.45; 0.00)	(-365.45; 0.00)
Range	(-6594.2; 5383.1)	(-6200.4; 8516.6)	(-8057.1; 5449.9)	(-8057.1; 8516.6)
p-value		< 0.001	< 0.001	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Subjects who prior to Week 6 had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes had their baseline value carried forward.
[c] Subjects who had insufficient data at Week 6 had their last value carried forward.

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Greater median reductions in fecal calprotectin concentration were observed for both doses in CRD3002 compared with the TNF antagonist failure population in CRD3001.

Study 3003:

At baseline, median fecal calprotectin concentrations were 493.48 µg/g, 191.06 µg/g, and 262.06 µg/g for the ustekinumab 90 mg q12w, q8w and placebo groups, respectively. At Weeks 24 and 44, the median change from baseline in fecal calprotectin was smaller in each ustekinumab group compared with the placebo group. At Week 44, the median change was 0.00 mg/kg for each ustekinumab groups, compared with the placebo group (153.85 µg/g, p=0.002 and p<0.001 for the q12w and q8w groups, respectively. Results are displayed in the following table:

TEFFECL03: Summary of the change from baseline in fecal calprotectin concentrations (µg/g) at Week 24 and Week 44; randomized subjects excluding those enrolled prior to study re-start

	placebo SC[a]	ustekinumab 90 mg SC q12w	ustekinumab 90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Baseline				
N	128	124	121	245
Mean (SD)	505.17 (760.789)	686.07 (1041.264)	500.79 (705.001)	594.57 (894.211)
Median	262.06	493.48	191.06	322.83
IQ range	(91.48; 591.31)	(97.07; 720.48)	(54.08; 577.25)	(70.21; 621.03)
Range	(11.9; 5446.3)	(11.9; 6241.3)	(11.9; 2817.8)	(11.9; 6241.3)
Change from baseline				
Week 24[b,c]				
N	127	124	121	245
Mean (SD)	354.44 (1521.640)	225.74 (1527.782)	-70.22 (699.964)	79.57 (1199.820)
Median	71.17	0.93	0.00	0.00
IQ range	(-66.17; 444.39)	(-174.87; 276.53)	(-137.59; 63.52)	(-139.65; 143.68)
Range	(-3208.4; 13347.4)	(-5203.9; 12279.9)	(-2322.3; 3169.0)	(-5203.9; 12279.9)
p-value		0.186	< 0.001	0.003
Week 44[b,c]				
N	127	123	121	244
Mean (SD)	413.47 (1382.975)	31.79 (1161.435)	-54.19 (634.347)	-10.85 (936.916)
Median	153.85	0.00	0.00	0.00
IQ range	(-18.30; 520.35)	(-179.35; 195.07)	(-134.30; 136.11)	(-156.11; 180.27)
Range	(-3208.4; 13347.4)	(-5616.3; 4939.9)	(-2410.8; 3169.0)	(-5616.3; 4939.9)
p-value		0.002	< 0.001	< 0.001

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint had their induction baseline value carried forward.
[c] Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward.

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Pyoderma Gangrenosum Assessment

All subjects were to be assessed for pyoderma gangrenosum. For subjects with pyoderma gangrenosum, the total number of lesions, size of primary lesion, and resolution were to be assessed.

Two subjects in the primary analysis population of this study had pyoderma gangrenosum. One subject in the placebo SC group and 1 subject in the ustekinumab 90 mg q12w group both experienced resolution of the primary lesion and reduction in the number of lesions.

Fistula Assessment

All subjects were to be assessed for fistulas. For subjects with fistulizing disease, fistula closure was to be assessed. A fistula response was defined as a ≥50% reduction in the number of draining fistulas. Enterocutaneous fistulas (eg perianal and abdominal) were to be considered no longer draining (ie closed) when there was an absence of drainage despite gentle compression.
Recto-vaginal fistulas were to be considered closed based on either physical examination or absence of relevant symptoms (eg passage of rectal material or flatus from the vagina).
'Fistula response' was not significantly different in the placebo and study drug groups over the 8 week induction studies.
Fistula response through Week 44 is summarized in the following table:

TEFFIST01: Number of subjects in fistula response at each visit through Week 44; randomized subjects excluding those enrolled prior to study re-start

		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Subjects with 1 or more fistulas at induction baseline	13	10	11	21
Week 0				
N	13	10	11	21
Subjects in fistula response	3 (23.1%)	4 (40.0%)	5 (45.5%)	9 (42.9%)
Week 4				
N	13	10	11	21
Subjects in fistula response	3 (23.1%)	6 (60.0%)	5 (45.5%)	11 (52.4%)
p-value		0.244	0.639	0.312
Week 8				
N	13	10	11	21
Subjects in fistula response	1 (7.7%)	6 (60.0%)	5 (45.5%)	11 (52.4%)
p-value		0.062	0.317	0.062
Week 12				
N	13	10	10	20
Subjects in fistula response	5 (38.5%)	7 (70.0%)	4 (40.0%)	11 (55.0%)
p-value		0.591	0.936	0.589
Week 16				
N	13	8	9	17
Subjects in fistula response	4 (30.8%)	6 (75.0%)	4 (44.4%)	10 (58.8%)
p-value		0.232	0.829	0.256
Week 20				
N	13	8	9	17
Subjects in fistula response	3 (23.1%)	6 (75.0%)	4 (44.4%)	10 (58.8%)
p-value		0.161	0.829	0.187
Week 24				
N	13	8	9	17
Subjects in fistula response	4 (30.8%)	6 (75.0%)	6 (66.7%)	12 (70.6%)
p-value		0.232	0.468	0.142
Week 28				
N	12	7	9	16
Subjects in fistula response	2 (16.7%)	6 (85.7%)	6 (66.7%)	12 (75.0%)
p-value		0.037	0.303	0.026
Week 32				
N	12	7	9	16
Subjects in fistula response	2 (16.7%)	6 (85.7%)	5 (55.6%)	11 (68.8%)

TEFFIST01: Number of subjects in fistula response at each visit through Week 44; randomized subjects excluding those enrolled prior to study re-start

		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
p-value		0.040	0.134	0.016
Week 36				
N	12	7	8	15
Subjects in fistula response	1 (8.3%)	6 (85.7%)	5 (62.5%)	11 (73.3%)
p-value		0.013	0.134	0.006
Week 40				
N	12	7	8	15
Subjects in fistula response	1 (8.3%)	6 (85.7%)	6 (75.0%)	12 (80.0%)
p-value		0.013	0.134	0.006
Week 44				
N	11	7	8	15
Subjects in fistula response	5 (45.5%)	5 (71.4%)	7 (87.5%)	12 (80.0%)
p-value		0.782	0.886	0.641

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.

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One or more clinically apparent fistulas were present at induction baseline in 8.8% of subjects in the primary analysis population.

At Week 0 of this study, after having received ustekinumab induction, 23.1% (n=3/13) and 42.9% (n=9/21) in the placebo and combined ustekinumab groups, respectively were in fistula response. The proportions of subjects who achieved fistula response were numerically greater in the combined ustekinumab compared with the placebo group at all timepoints.

At Week 44, 80.0% (n=12/15) of subjects in the combined ustekinumab groups had a fistula response compared with 45.5% (n=5/11) in the placebo group.

Health-related quality of life

Health-related quality of life was assessed by IBDQ and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo.

Clinical studies in special populations

The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn's Disease. No separate studies have been carried out in special populations the SmPC includes relevant statements in this regard for the prescriber – this is acceptable. Use in patients with hepatic impairment and with renal impairment is 'missing information' in the RMP

Table 8: Number of subjects by age group in Crohn's disease clinical studies; Randomized subjects in C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003

	Age (years)			
	< 65 (n/N) [a]	65-74 (n/N) [a]	75-84 (n/N) [a]	>= 85 (n/N) [a]
Analysis set: Randomized subjects in C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003	1932	61	5	-
C0379T07 (Population 1)	100/104	4/104	0/104	-
C0743T26	507/526	16/526	3/526	-
CNTO1275CRD3001[b]	724/741	17/741	0/741	-
CNTO1275CRD3002[b,c]	601/627	24/627	2/627	-
CNTO1275CRD3003[b]	373/388	15/388	0/388	-

[a] n: number of the randomized subjects in the specified age group; N: total number of randomized subjects in the study.
[b] Excluding subjects enrolled prior to study restart.
[c] Excluding subjects from site 1127

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Overall, 66/1998 subjects were ≥65 years of age, with 5/1998 subjects being 75 to 84 years of age. No subjects in these studies were ≥85 years of age.

Supportive study

Subjects from participating sites within the Phase 3 development program could consent to participate in the endoscopy substudy and undergo endoscopic assessments at screening (induction baseline), at the end of the induction study (Week 8 of induction), and at the end of the maintenance study (Week 44 of maintenance).

334 of 1409 subjects in the induction studies were enrolled in this sub-study, including 142 subjects in CRD3001 and 192 subjects in CRD3002.

Baseline characteristics of subjects in the endoscopy sub-study induction population were similar to those of the overall induction study population in term so of baseline demographic / disease / Crohn's medication characteristics as well as for baseline endoscopy findings.

Two measures were used for the evaluation of endoscopic healing of the mucosa:

- changes in the Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD) score and detection of presence/absence of mucosal ulceration.
- biopsies were collected to support exploratory histologic evaluation.

Mucosal Healing was defined as the complete absence of any mucosal ulcerations among subjects who presented with ulceration in at least 1 ileo-colonic segment at induction baseline.

Endoscopic Response was defined as a reduction of ≥50% from induction baseline in SES-CD score.

Endoscopic Remission was defined as a total SES-CD score of ≤2.

The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of

ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures.
At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p=0.012).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design of all 3 phase III clinical studies is considered adequate, the patient population is adequately selected and the comparator (placebo) is appropriate. The different arms of each study were balanced at baseline with regards to subject demographics, disease characteristics, relevant medical history and prior therapies and concomitant medications; this is acceptable.

For studies CRD3001 and CRD3002, the primary end-point was clinical response at 6 weeks after administration of Stelara. Guideline on the development of new medicinal products for the treatment of Crohn's disease, CPMP/EWP/2284/99 Rev. 1, July 2008 advises a primary end-point of:

> *The proportion of patients achieving remission within the period of about four to eight weeks, based on the pharmacodynamic properties of the test drug*

And that

> *Active treatment should continue for at least eight weeks or for at least 2 cycles of therapy depending on which is the longer.*

The chosen primary end-point does not comply with current CHMP guidance regarding duration of study. In order to comply with CHMP guidance, it would have been preferred if the company had chosen a primary end-point of clinical remission at 16 weeks (2 cycles of therapy). Yet it is acknowledged that the clinical development of Stelara in the indication of Crohn's disease was initiated before the final version of the current guideline was published given these circumstances the chosen endpoint is considered acceptable.

Secondary end-points were: clinical remission at Week 8, clinical response at Week 8, 70-point response at Week 6 and 70-point response at Week 3. It would have been preferred for clinical remission at week 8 to be the primary end-point (using a week 8 end-time). It is acknowledged that the 70-point reductions in CDAI scores reflect advice from Points to consider on clinical investigation of medicinal products for the management of Crohn's disease, CPMP/EWP/2284/99, June 2001 (superseded by Rev 1, July 2008). The company also assayed laboratory measurements of inflammation (serum CRP concentration and fecal content of calprotectin), the IBDQ and SF-36 questionnaires were conducted, an endoscopy sub-study was done, fistula response was assessed; these measurements are advised in Guideline on the development of new medicinal products for the treatment of Crohn's disease, CPMP/EWP/2284/99 Rev. 1, July 2008 and are acceptable.

For study CRD3003, the primary end-point was clinical remission at Week 44 where clinical remission is defined as a CDAI score of <150 points.

Guideline on the development of new medicinal products for the treatment of Crohn's disease, CPMP/EWP/2284/99 Rev. 1, July 2008 advises a primary end-point of:

> *the proportion of patients in whom steroid-free remission is maintained without surgery throughout at least 12 months*

Although the chosen primary end-point differs from that recommended by the CHMP, it is acknowledged that the company had chosen to develop Stelara for a population that had not achieved a successful outcome with currently available therapies and for whom options were therefore restricted. In this context, a primary end-point of clinical remission is considered to be clinically important.

The primary end-point was assessed at 44 weeks. CPMP/EWP/2284/99 Rev. 1 advises:

> *The treatment period should be aimed at a minimum of 12 months. A follow-up period of 3 months after treatment discontinuation should be included in the trial.*

The chosen primary end-point does not fully comply with current CHMP guidance regarding duration of study. Nonetheless, it is acknowledged that the company is conducting a 228 week extension study of CRD3003 with the objective to evaluate primarily the long-term safety of ustekinumab as described in the RMP which is considered acceptable.

Secondary end-points were: clinical response at Week 44, clinical remission at Week 44 among subjects in clinical remission to ustekinumab at Week 0, corticosteroid-free remission at Week 44, clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF-antagonist therapy (ie subjects from induction study CRD3001).

Steroid-free remission analysis was also performed with the additional requirement of no steroid use for a minimum of 30 and also 90 days prior to the Week 44 primary maintenance endpoint; this is acceptable and is considered to be more informative than a point measurement at week 44.

The company assayed laboratory measurements of inflammation (serum CRP concentration and faecal content of calprotectin), the IBDQ and SF-36 questionnaires were conducted, an endoscopy sub-study was done. These measurements are consistent with requirement in the guideline CPMP/EWP/2284/99 Rev. 1.

Clinical assessment of fistula drainage was a secondary end-point, as advised in the guideline CPMP/EWP/2284/99 Rev. 1.

Efficacy data and additional analyses

There were 741 subjects randomised in study CRD3001.

For the primary endpoint of clinical response at Week 6, a higher proportion of subjects in the ~6 mg/kg ustekinumab and 130 mg ustekinumab groups were in clinical response at Week 6 (33.7% and 34.3%, respectively) compared with the placebo group (21.5%; p=0.003 and p=0.002, respectively). The study met its primary end-point.

For the secondary endpoint of clinical remission at Week 8, a higher proportion of subjects in the ~6 mg/kg ustekinumab and 130 mg ustekinumab groups were in clinical remission at Week 8 (20.9% and 15.9%, respectively) compared with the placebo group (7.3%; p<0.001 and p=0.003, respectively).

Clinical remission and response were evident from week 3 onwards.

Other secondary end-point results and sensitivity analyses were supportive towards the primary end-point.

There were 627 subjects randomised in study CRD3002.

For the primary endpoint of clinical response at Week 6, a higher proportion of subjects in the ~6 mg/kg ustekinumab and 130 mg ustekinumab groups were in clinical response at Week 6 (55.5% and 51.7%, respectively) compared with the placebo group (28.7%; both p<0.001). The study met its primary end-point.

For the secondary endpoint of clinical remission at Week 8, a higher proportion of subjects in the ~6 mg/kg ustekinumab and 130 mg ustekinumab groups were in clinical remission at Week 8 (40.2% and 30.6%, respectively) compared with the placebo group (19.6%; p<0.001 and p=0.009, respectively).

Clinical remission and response were evident from week 3 onwards. Other secondary end-point results and sensitivity analyses were supportive towards the primary end-point.

While both the 130 mg and the ~6 mg/kg dose provided rapid, meaningful clinical benefit across a range of endpoints in the broad Crohn’s disease population, the totality of the evidence across clinical outcomes, suggested that the ~6 mg/kg dose performed better than the 130 mg dose. These differences were most notable in clinical remission at Week 8,especially since the 130 mg group started to lose response between Weeks 6 and 8 while the ~6 mg/kg dose was stable or continued to improve. Although these differences were most apparent in the population that had failed conventional therapy, they were also observed in the TNF-antagonist refractory population with more severe disease. Differences in efficacy between the doses were supported by exposure-response analyses showing that the ~6 mg/kg dose shifted more patients into exposure thresholds associated with higher response rates. Importantly, the ~6 mg/kg dose did not have notable safety differences compared with the lower dose over 8 weeks in pooled analyses.

397 subjects went forward to be randomised in study CRD3003.

For the primary endpoint of clinical remission at Week 44, a higher proportion of subjects in the 90mg ustekinumab QW8 and 90mg ustekinumab QW12 groups were in clinical remission at Week 44 (53.1% and 48.8%, respectively) compared with the placebo group (35.9%; p=0.005 and p=0.040, respectively). The study met its primary end-point.

For the secondary endpoint of clinical response at Week 44, a higher proportion of subjects in the 90mg ustekinumab QW8 and 90mg ustekinumab QW12 groups were in clinical response at Week 44

(59.4% and 58.1%, respectively) compared with the placebo group (44.3%; p=0.018 and p=0.033, respectively).

Subjects receiving corticosteroids at Week 0 of the maintenance study who were in clinical response underwent reduction of corticosteroid intake from Week 0.

The major secondary endpoint of corticosteroid-free remission at Week 44 in CRD3003 was achieved by a greater proportion of subjects in the ustekinumab 90 mg q12w and q8w groups (42.6% and 46.9%, respectively) compared with the placebo group (29.8%). While the nominal p-values for the comparisons of each of the ustekinumab groups with placebo were <0.05 for this endpoint, only the ustekinumab 90 mg q8w regimen can be considered as significantly different from placebo (p=0.004) within the global testing procedure. Nevertheless, ancillary analyses of steroid intake are generally supportive towards Stelara exposure permitting reduction in steroid intake. The proportions of subjects in the placebo group that were in remission and off steroids for 30 and 90 days (29.8% and 29%, respectively) were lower than in the 90 mg q12w (42.6% and 41.1%, respectively) as well as lower than the 90 mg q8w group (46.9% and 45.3%, respectively; p<0.05 for all comparisons vs placebo).

Other secondary end-point results and sensitivity analyses were supportive towards the primary end-point.

Taken together the efficacy results for those who received Stelara q8W and q12W in study CRD3003 both were superior to placebo;

In study CRD3003, the increase in absolute rate of clinical remission at week 44 for q8w administration versus q12w was 4.3% (rate ratio 1.09) and the increase in absolute rate of clinical response at week 44 for q8w administration versus q12w was 1.3% (rate ratio 1.02).In contrast, there was more evidence of 'related' adverse events with q8W dosing versus q12W dosing. The CHMP considered that the increased rate of adverse events associated with q8W dosing counterbalances the increased efficacy such that the q8W and q12W bring equivalent risk/benefit balances. Therefor the s.c. standard dose was amended to dosing every 12 weeks (with potential increase to q8w in case if inadequate response. However, as the company provided evidence that 31 subjects [median CDAI = 340, i.e. 'high burden of disease] experienced loss of response before their second maintenance dose arguing that waiting to receive a second subcutaneous dose at week 12 was too long for these subjects who were placed on a Q8W dosage. When assessed 16 weeks later (after 2 Q8W ustekinumab administrations), the company states that 15/31 were back in clinical response, suggesting that Q8W maintenance dosing was a preferable regimen for 15/31 of these patients. Although this analysis of the company is observational, it is noted that the company carried out a re-analysis of data on subjects who had lost response as part of the original submission; when analysed as a treatment strategy (that preserved initial randomisation), similar rates of clinical response and remission were confirmed between subjects initiating q12w dosing but being allowed to switch to q8w dosing frequency, and those patients who received q8w dosing from the start.

In the context of a disease such as Crohn's disease, the CHMP agrees that to offer patients who have inadequate response at an early stage of exposure a posology of 8QW is acceptable.

Results indicated further that subjects receiving an ustekinumab 90 mg q12w dose regimen who have experienced a decrease in their response during maintenance, may benefit from an increase in dosing frequency to 90 mg q8w, and that taking the approach of initiating subjects on 90 mg q12w with adjustment to q8w when needed by LOR ultimately results in similar clinical outcomes to simply starting all subjects on 90 mg q8w. This supports further the rationale to have the ability to increase the maintenance dose frequency from q12w to q8w upon loss of response in subjects who would begin maintenance therapy with a q12w regimen.

As 50% of the ustekinumab induction non-responders attained response after an additional ustekinumab 90 mg SC dose, there is a demonstrated benefit of receiving an additional dose 8 weeks after induction. Further, a substantial number of these subjects maintained response and were in remission at Week 44, indicating benefit from continued maintenance therapy with ustekinumab in delayed responders. The SmPC outlines that consideration should be given to discontinuation of the treatment in patients who show no evidence of therapeutic benefit by week 16 or 16 weeks after switching to the 8-weekly dose.

At visits from Week 4 to Week 44, median CDAI scores were maintained over time for subjects in the ustekinumab groups while scores increased over time for subjects in the placebo group, notably after Week 16.

There was a decline in the proportions of subjects in clinical response during the maintenance phase. The proportions of subjects in clinical response in the ustekinumab groups were comparable and decrease from Week 0 of this study through Week 28 and plateau at approximately 60% through Week 44. The proportions of subjects in the placebo group in clinical response decreased over time with separation from the ustekinumab groups clearly observed by Week 20, and the greatest separation from treatment groups occurring after Week 28 and continuing through Week 44.

As a post hoc exercise, durable clinical remission was defined by the company as requiring subjects to be in remission at 80% of visits prior to Week 44 and also at Week 44 (i.e. at least 9 of 11 visits in the CRD3003 study). This analysis was performed in subjects who were in clinical response at baseline in study CRD3003. Results are shown in the following table:

Table 13: Number of subjects in durable clinical remission; Randomized subjects in CNTO1275CRD3003 excluding those enrolled prior to study restart

		Ustekinumab		
	Placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects in CNTO1275CRD3003 excluding those enrolled prior to study restart	131	129	128	257
Subjects in durable clinical remission[b,c,d]	31 (23.7%)	44 (34.1%)	51 (39.8%)	95 (37.0%)
p-value		0.068	0.003	0.005

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to a designated visit (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 or 44), except for Week 0, are considered not to be in clinical remission, regardless of their CDAI score.
[c] Subjects who had insufficient data to calculate the CDAI score a designated visit (Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 or 44) are considered not to be in clinical remission.
[d] Durable clinical remission: Clinical remission at ≥ 80 % of all visits (at least 9 out of 11) and in clinical remission at the last visit (Week 44).

[TEUEFCREM01B.RTF] [CNTO1275\Z ADHOC REQ\DBR 2016 03 CD\RE EMA 201603\PROD\TEUEFCREM01B.SAS] 06APR2016, 07:55

A statistically significant result was reached for the ustekinumab q8w dose regimen, and while statistical significance was not met for the ustekinumab q12w dose regimen, a generally similar effect size was seen as in the primary analysis. Results are consistent with the primary endpoint of study CRD3003.However as the analysis of 'durable clinical remission' was presented by the company as a post hoc exercise the CHMP did not agree to include this information in the SmPC. The Applicant will

further examine the proportion of subjects in remission over the course of the long-term extension (from Week 44 onwards) as outlined in the RMP and submit the study results for assessment as soon as available.

A post hoc analysis of study CRD3003 supports a conclusion that there are advantages by switching from Q12W maintenance therapy to Q8W maintenance therapy where there has been loss of response.

Data are also submitted that suggest that, for subjects who responded to the ustekinumab IV induction dose but delayed initiation of the SC maintenance therapy, benefit can be regained without the need for an additional IV induction dose [the company acknowledges that there were only 51 subjects in this group and that most had a dose adjustment within the first 16 weeks of the maintenance study i.e. data are limited].

142 subjects in CRD3001 and 192 subjects in CRD3002 were enrolled in an endoscopy sub-study. The baseline characteristics of subjects in the endoscopy sub-study induction and maintenance study populations were similar to those of the overall induction and maintenance study populations.

Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in the sub-study. At week 8, after a single intravenous induction dose, the primary endpoint of change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. The change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p=0.012).

95 subjects went forward for endoscopy in study CRD3003. A statistically significant difference in SES-CD score between study drug and placebo groups was not found at week 44. The high fall-out of subjects over the maintenance study and consequent potential for selection bias makes it difficult to interpret results from the maintenance phase. Histological analysis of mucosal biopsies did not convince of an effect of Stelara.

In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as $\geq$ 50% reduction from baseline in the number of fistulae draining upon gentle compression) compared to 5/11 (45.5%) exposed to placebo.

For those exposed to Stelara, both serum CRP concentration and fecal content of calprotectin fell over the first 8 weeks of induction compared to placebo, presumably reflecting a reduction in inflammatory burden for those who received Stelara. Thereafter in the maintenance phase, both serum CRP concentration and fecal content of calprotectin were relatively stable over the course of 44 weeks in those who received Stelara. Further post hoc subgroup analyses indicated that patients with lower inflammatory burden (e.g. CRP ≤10mg/mL) may also benefit from a every 12 week dosing. However as this subgroup analysis was not pre-specified (lack ability to control type I errors and to lack adequate power) the CHMP considered this an exploratory finding only.

For those exposed to Stelara, both the IBDQ and SF-36 scores rose over the first 8 weeks of induction compared to results for the placebo group. Scores were relatively constant thereafter in the Stelara group over the course of the 44 week maintenance phase. Further, the results of the work limitations questionnaire, time lost from work questionnaire and the productivity visual analogue scale did not convince of difference between the Stelara and placebo groups over the course of the maintenance phase.

Results submitted by the company in 3 technical reports for serum protein and biopsy transcriptome analyses are considered exploratory and hypothesis generating and to be not of a standard required for inclusion in the PI texts.

There is lack of information on exposure to the paediatric population and pregnant women; this is reflected in the proposed SmPC which is acceptable. The company also clarified that the numbers of elderly who were exposed to Stelara were low. Overall, 66/1998 subjects were ≥65 years of age, with 5/1998 subjects being 75 to 84 years of age. No subjects in these studies were ≥85 years of age. No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients and during use to date in the psoriasis and psoriatic arthritis indications, no safety concern relating to use in the elderly has been included in the RMP. It is therefore considered by the CHMP that statements in the SmPC to raise to the prescriber that the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients are appropriate.

2.5.4. Conclusions on the clinical efficacy

The primary end-point of clinical remission over extended exposure to Stelara for 44 weeks in the maintenance study was met for both q8W and q12w regimens. This is considered to be clinically important for subjects with Crohn's disease and who have been unable to take anti-TNF or immune-modulator medicinal products.

Results of secondary end-points support the primary end-point. In particular, exposure to Stelara was associated with decreased exposure to oral steroids. This is also considered to be clinically important for subjects with Crohn's disease because of the significant adverse event profile associated with steroids.

Taken together the efficacy results for those who received Stelara q8W and q12W in study CRD3003 both were superior to placebo. In study CRD3003, the increase in absolute rate of clinical remission at week 44 for q8w administration versus q12w was 4.3% (rate ratio 1.09) and the increase in absolute rate of clinical response at week 44 for q8w administration versus q12w was 1.3% (rate ratio 1.02).

The CHMP considered the increased efficacy with q8W dosing as counterbalanced by more evidence of 'related' adverse events with q8W dosing versus q12W dosing. The company's proposal to initiate dosing every 8 weeks in patients with high burden of disease (CRP >10mg/L and / or CDAI ≥350) was not accepted by the CHMP as supportive data were based on post hoc subgroup analyses. Therefor the s.c. standard dose (after the first s.c. dose applied 8 weeks after the intravenous dose) was amended to dosing every 12 weeks (with potential increase to q8w in case of inadequate response). To avoid early loss of response, patients who have not shown adequate response at 8 weeks after the first subcutaneous dose may receive a second subcutaneous dose at this time.

It can be concluded that Stelara brings clinical efficacy to those subjects with Crohn's disease who have failed to respond or who are intolerant towards anti-TNF or conventional therapy.

2.6. Clinical safety

Patient exposure

Crohn's disease

The clinical development program for ustekinumab in Crohn's disease consists of the following studies:

- One Phase 2a proof-of-concept study (C0379T07).

- One Phase 2b dose-ranging study (C0743T26).
- Two Phase 3 induction studies (CNTO1275CRD3001 and CNTO1275CRD3002).
- One Phase 3 randomized withdrawal maintenance study (CNTO1275CRD3003).

The safety database from the 5 Crohn's disease clinical studies comprises 1749 ustekinumab-treated subjects (a total of 1106 subject years of follow-up) and includes 849 subjects exposed for at least 6 months, and 464 subjects exposed for at least 1 year. Of these 1749 subjects:

- 1664 subjects received a single IV induction dose of ustekinumab at Week 0 (601 received ~6 mg/kg; 754 received 130 mg; and 309 received other doses).
- 1205 subjects received ustekinumab 90 mg SC maintenance dosing (every 8 or 12 weeks).

Table 6: Summary of duration of ustekinumab exposure through one year of follow up; treated subjects in Crohn's disease studies[a]

	Crohn's Disease[b]
	Ustekinumab
Subjects treated with ustekinumab	1749
Duration of ustekinumab exposure	
Single IV	1664 (95.1%)
At least 6 months[c]	849 (48.5%)
At least 1 year[d]	464 (26.5%)
Avg duration of treatment (weeks)	19.48
Total subject-years of follow-up	1106
Total dose (mg)	
N	1749
Mean (SD)	432.1 (243.86)
Median	399.6
IQ range	(219.6; 619.2)
Range	(3; 1060)

SD=standard deviation

[a] C0379T07(only placebo-controlled IV population in population 1; through Week 28), C0743T26 (through Week 36), CNTO1275CRD3001 (through Week 8 for subjects who entered CNTO1275CRD3003; through Week 20 for subjects who did not enter CNTO1275CRD3003), CNTO1275CRD3002 (through Week 8 for subjects who entered CNTO1275CRD3003; through Week 20 for subjects who did not enter CNTO1275CRD3003), CNTO1275CRD3003 (through Week 44).

[b] Placebo crossover subjects were included in the ustekinumab columns after crossover to ustekinumab.

[c] The duration between the first and last ustekinumab administration was at least 14 weeks.

[d] The duration between the first and last ustekinumab administration was at least 38 weeks.

SOURCE: [TSFINFE91A.RTF] [CNTO1275\Z_SCS\DBR_2015_07\RE_2015_07\PROD\TSFINFE91A.SAS] 09OCT2015, 16:07: TSFEXP02A.RTF] [CNTO1275\Z_SCS\DBR_2015_07\RE_2015_07\PROD\TSFEXP02A.SAS] 09OCT2015, 16:01

Pooled indications (psoriasis, psoriatic arthritis and Crohn's disease)

Through 1 year of follow-up across all pooled indications (psoriasis, psoriatic arthritis and Crohn's disease), 5,884 subjects were treated with ustekinumab with 4,521 subject-years of follow-up.

Of these subjects, 3,503 received a 90 mg SC dose of ustekinumab either q8w or q12w (1,205 subjects in the combined Crohn's disease studies, 1801 subjects in the combined psoriasis studies, and 497 subjects in the combined PsA studies.

Through 5 years across all pooled indications (psoriasis, psoriatic arthritis and Crohn's disease), 5,884 subjects were treated with ustekinumab (1,749 subjects in the combined Crohn's disease studies, 3,117 subjects [533 on 90 mg SC q8w] in the combined psoriasis studies, and 1,018 in the combined psoriatic arthritis studies) with a total of 10,954 subject years of follow-up.

Data are summarised in the following table:

Table 8: Summary of duration of ustekinumab exposure and total ustekinumab dose through 1 year of follow-up for Crohn's disease and PsA studies and through 5 years of follow-up for psoriasis studies

	Crohn's Disease[a]	Psoriasis[b]	PsA[c]
	Ustekinumab	Ustekinumab	Ustekinumab
Subjects treated with ustekinumab	1749	3117	1018
Subject years of follow-up	1106	8998	850
Duration of ustekinumab exposure			
Single IV	1664 (95.1%)	0	0
At least 6 months	849 (48.5%)	2413 (77.4%)	842 (82.7%)
At least 1 year	464 (26.5%)	1855 (59.5%)[d]	527 (51.8%)
At least 2 years	NA	1653 (53.0%)	NA
At least 3 years	NA	1569 (50.3%)	NA
At least 4 years	NA	1482 (47.5%)	NA
At least 5 years	NA	838 (26.9%)	NA
Avg duration of treatment (weeks)	19.48	128.89	27.66

IV=intravenous; NA=not applicable; Pbo=placebo; PsA=psoriatic arthritis; UST=ustekinumab; W=week.
a: C0379T07 (only pbo-controlled IV population in Population 1; through W28), C0743T26 (through W36), CRD3001 and CRD3002 (through W8 for subjects who entered CRD3003; through W20 for subjects who did not enter CRD3003), CRD3003 (through W44).
b: C0379T04 (through W52), C0743T08 (through W264), C0743T09 (through W264), C0743T12 (through W64).
c: C0743T10 (through W36), CNTO1275PSA3001 (through W52), CNTO1275PSA3002 (through W60).
d: Psoriasis data for at least 1 year and onward as reported in 5-year Update.
Adapted from: TSFEXP02A, TSFINFE91A [CNTO1275\Z_SCS\DBR_2015_07\RE_2015_07\PROD]; S_EXP_73_A [5-Yr Update PSO -EU/MOW RE603]; S_INFE_14_B [5-YR Update PSO-EU/MOW/Mod2.7.4/Tab10/ RE603]

Adverse events

Pooled Data from Phase 3 Studies

The average duration of follow-up and average exposure was similar for subjects in the placebo, ustekinumab 130 mg IV, and ustekinumab ~6 mg/kg IV groups, during the placebo-controlled period (0-8 weeks) in the combined Phase 3 induction studies (CRD3001 and CRD3002).

The overall proportions of subjects with AEs were comparable between treatment groups with no evidence of a dose effect (60.5% in the placebo group, 58.4% in the ustekinumab 130 mg IV group, and 60.4% in the ustekinumab ~6 mg/kg IV group).

The SOCs with the highest proportions of AEs that occurred in subjects in the combined ustekinumab group were Gastrointestinal Disorders (26.4% in the placebo group and 22.3% in the combined ustekinumab group) and Infections and Infestations (22.1% in the placebo group and 22.0% in the combined ustekinumab group); the proportions of subjects in these SOCs were comparable between treatment groups and there was no evidence of a dose effect between the 2 ustekinumab dose groups.

Pooled key data of the induction phase are summarised in the following table:

Key Safety Events for Crohn's Disease Studies: Induction Phase (Phase 3 Studies)

Table 1: Summary of key safety events during placebo-controlled induction (Week 0 to Week 8); treated subjects in Phase 3 Crohn's disease studies (CNTO1275CRD3001 and CNTO1275CRD3002)

		Ustekinumab		
	Placebo	130 mg	6 mg/kg	Combined
Subjects treated	466	471	470	941
Avg duration of follow-up (weeks)	8.18	8.22	8.16	8.19
Avg exposure (number of administrations)	1.00	1.00	1.00	1.00
Subjects who died	0	0	0	0
Subjects who discontinued because of 1 or more adverse events	19 (4.1%)	8 (1.7%)	8 (1.7%)	16 (1.7%)
Total number of subjects with				
Adverse events	282 (60.5%)	275 (58.4%)	284 (60.4%)	559 (59.4%)
Serious adverse events	28 (6.0%)	23 (4.9%)	25 (5.3%)	48 (5.1%)
Infections[a]	108 (23.2%)	92 (19.5%)	111 (23.6%)	203 (21.6%)
Serious Infections[a]	6 (1.3%)	7 (1.5%)	8 (1.7%)	15 (1.6%)
AEs temporally associated with infusions	11 (2.4%)	17 (3.6%)	12 (2.6%)	29 (3.1%)
Malignancies (excluding NMSC)	0	0	0	0

AEs=adverse events; NMSC=nonmelanoma skin cancer
[a] Infection as assessed by the investigator.

Adapted from: [TSFKEY01A.RTF] [CNTO1275\Z_SCS\DBR_2015_07\RE_2015_07\PROD\TSFKEY01A.SAS] 09OCT2015, 16:09

A 1% difference in the proportion of subjects with the AEs of asthenia and acne between the ustekinumab ~6 mg/kg IV and placebo groups and an approximately 2.5-fold greater number of events in ustekinumab-treated subjects could be observed.

The was a 1.7% difference in the proportion of subjects with the AE of vomiting between the ustekinumab ~6 mg/kg IV and placebo groups and an approximate 1.5 fold greater number of events in the ustekinumab ~6 mg/kg IV group.

An extract of table TSFAE01A showing the frequencies of asthenia, acne and vomiting is shown:

TSFAE01A: Number of subjects with 1 or more treatment-emergent adverse events during placebo-controlled induction (Week 0 to Week 8) by MedDRA system-organ class and preferred term; treated subjects in Phase 3 Crohn's disease studies (CNTO1275CRD3001 and CNTO1275CRD3002)

		Ustekinumab		
	Placebo	130 mg	6 mg/kg	Combined
Subjects treated	466	471	470	941
Avg duration of follow-up (weeks)	8.18	8.22	8.16	8.19
Avg exposure (number of administrations)	1.00	1.00	1.00	1.00
Total number of subjects with adverse events	282 (60.5%)	275 (58.4%)	284 (60.4%)	559 (59.4%)
Asthenia	2 (0.4%)	4 (0.8%)	7 (1.5%)	11 (1.2%)

Acne	2 (0.4%)	2 (0.4%)	5 (1.1%)	7 (0.7%)
Vomiting	12 (2.6%)	14 (3.0%)	20 (4.3%)	34 (3.6%)

Pooled Data from Phase 2 and Phase 3 Studies were consistent with that observed in the primary analysis (using Phase 3 data alone).

Maintenance Phase

The average duration of follow-up in study CRD3003 was similar for randomized subjects who received placebo, ustekinumab 90 mg SC q12w, or ustekinumab 90 mg SC q8w.

The overall proportions of subjects with AEs were comparable amongst treatment groups with no evidence of a dose effect between the 2 ustekinumab dose groups (83.5% in the placebo group, 80.3% in the ustekinumab 90 mg SC q12w group, and 81.7% in the ustekinumab 90 mg SC q8w group).

The SOCs with the highest proportions of AEs in the combined ustekinumab group during maintenance were Infections and Infestations (48.9% of subjects in the placebo group and 46.8% of subjects in the combined ustekinumab group) and Gastrointestinal Disorders (47.4% of subjects in the placebo group and 39.2% of subjects in the combined ustekinumab group) with no evidence of dose effect between the 2 ustekinumab dose groups.

The higher proportion of subjects in the placebo group who experienced AEs in the Gastrointestinal Disorders SOC compared with subjects in the combined ustekinumab group is not unexpected given the nature of the underlying disease when untreated.

Pooled key data are summarised in the following table:

Key Safety Events for Crohn's Disease Studies: Maintenance Phase (Phase 3 Study)

Table 2: Summary of key safety findings through Week 44 or up to the time of dose adjustment; treated subjects who were randomized in Phase 3 Crohn's disease study CNTO1275CRD3003

	placebo SC[a,b]	ustekinumab[b] 90 mg SC q12w	ustekinumab[b] 90 mg SC q8w	Combined
Analysis set: Treated subjects who were randomized	133	132	131	263
Average duration of follow-up (weeks)	32.0	36.6	35.2	35.9
Subjects who died	0	0	0	0
Total number of subjects with treatment emergent				
Adverse events	111 (83.5%)	106 (80.3%)	107 (81.7%)	213 (81.0%)
Serious adverse events	20 (15.0%)	16 (12.1%)	13 (9.9%)	29 (11.0%)
Infections [c]	66 (49.6%)	61 (46.2%)	63 (48.1%)	124 (47.1%)
Serious infections [c]	3 (2.3%)	7 (5.3%)	3 (2.3%)	10 (3.8%)
Adverse events leading to discontinuation of study agent	8 (6.0%)	10 (7.6%)	4 (3.1%)	14 (5.3%)

q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into the maintenance study.
[b] Includes data up to the time of dose adjustment (ie, time of meeting loss of response criteria).
[c] Infection as assessed by the investigator.

[TSFAE13A.rtf] [CNTO1275\CRD3003\DBR_CSR\RE_CSR\tsfae13a.sas] 07OCT2015, 18:01

A 2% difference in the proportion of subjects with the AE of vulvovaginal mycotic infection between the ustekinumab 90 mg SC q8w and placebo SC groups, together with a 4-fold greater number of events in the ustekinumab q8w group supporting the determination of vulvovaginal mycotic infection could be observed.

An extract of table TSFAE01A showing the frequency of vulvovaginal mycosis is shown:

TSFAE01A: Number of subjects with 1 or more treatment-emergent adverse events through Week 44 or up to the time of dose adjustment by MedDRA system-organ class and preferred term; treated subjects who were randomized

		ustekinumab[b]		
	placebo SC[a,b]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Treated subjects who were randomized	133	132	131	263
Average duration of follow-up (Weeks)	32.0	36.6	35.2	35.9
Total number of subjects with 1 or more treatment-emergent adverse events	111 (83.5%)	106 (80.3%)	107 (81.7%)	213 (81.0%)
Vulvovaginal mycotic infection	1 (0.8%)	1 (0.8%)	4 (3.1%)	5 (1.9%)

Pooled Data from Phase 2 and Phase 3 Studies were consistent with that observed in the primary analysis (using Phase 3 data alone).

Safety for Combined Induction and Maintenance Phases (Up to 1 Year)

Analyses were conducted combining data from the induction and maintenance phases of the Phase 3 studies. These analyses were conducted on randomized subjects up to the time of dose adjustment and provide data for up to a total of 52 weeks of follow-up.

Key safety events for up to 52 weeks of exposure show no evidence of a dose effect between treatment groups for each high-level safety topic, including the subgroup of subjects who received the recommended dosing regimen for Crohn's disease (6 mg/kg IV induction followed by 90 mg SC q8w or q12w), as shown in table 9:

Table 9: Summary of key safety events on induction and maintenance therapy (up to 52 weeks total) presented as subjects per hundred subject-years of follow-up; treated subjects randomized as responders to ustekinumab in Phase 3 Crohn's disease study (CNTO1275CRD3003)

		Ustekinumab maintenance		
	Placebo maintenance[a]	90 mg q12w[a]	90 mg q8w[a]	Combined
Subjects treated	133	132	131	263
Avg duration of follow-up (weeks)	40.10	44.89	43.29	44.09
Avg duration of treatment (weeks)	34.75	34.64	37.06	35.85
Total subject-years of follow-up	103	114	109	223
Number of subjects (with key safety event) per 100 subject-years				
Adverse events	112.13	100.05	107.29	103.59
Serious adverse events	21.45	16.67	16.51	16.59
Infections[b]	75.08	62.31	70.61	66.37
Serious Infections[b]	3.90	7.90	3.67	5.83

Avg=average; q8w=every 8 weeks; q12w=every 12 weeks
[a] Includes data up to the time of meeting loss of response criteria for dose adjustment.
[b] Infection as assessed by the investigator.

SOURCE: TSFAE41b; TSFSAE41b; TSFINFE41b; TSFINFE42b: 09OCT2015

Pooled Data from Phase 2 and Phase 3 Studies were consistent with that observed in the primary analysis (using Phase 3 data alone).

Extracts of Data for all subjects treated within maintenance study CRD3003, (including both randomized and nonrandomized subjects) are shown below:

TSFAE01F: Number of subjects with 1 or more treatment-emergent adverse events through Week 44 by MedDRA system-organ class and preferred term; treated subjects

		ustekinumab			
			Non-responders to IV induction dosing		
	placebo SC[a]	Responders to ustekinumab IV induction dosing[b]	Subsequent responders at Week 8 of maintenance → continue ustekinumab SC[c]	Subsequent non-responders at Week 8 of maintenance → discontinue at Week 8[d]	All ustekinumab
Analysis set: Treated subjects	242	396	419	342	1157
Avg duration of follow-up (weeks)	34.0	30.0	41.9	18.7	30.9
Total number of subjects with 1 or more treatment-emergent adverse events	198 (81.8%)	297 (75.0%)	361 (86.2%)	211 (61.7%)	869 (75.1%)
System-organ class/preferred term					
Infections and infestations	117 (48.3%)	171 (43.2%)	233 (55.6%)	80 (23.4%)	484 (41.8%)
Gastrointestinal disorders	116 (47.9%)	150 (37.9%)	208 (49.6%)	101 (29.5%)	459 (39.7%)
Musculoskeletal and connective tissue disorders	64 (26.4%)	98 (24.7%)	107 (25.5%)	42 (12.3%)	247 (21.3%)
Skin and subcutaneous tissue disorders	31 (12.8%)	81 (20.5%)	99 (23.6%)	33 (9.6%)	213 (18.4%)
Rash	8 (3.3%)	19 (4.8%)	14 (3.3%)	12 (3.5%)	45 (3.9%)
Pruritus	2 (0.8%)	11 (2.8%)	12 (2.9%)	3 (0.9%)	26 (2.2%)
Acne	1 (0.4%)	7 (1.8%)	8 (1.9%)	4 (1.2%)	19 (1.6%)
Alopecia	1 (0.4%)	6 (1.5%)	10 (2.4%)	0	16 (1.4%)
Eczema	2 (0.8%)	3 (0.8%)	7 (1.7%)	1 (0.3%)	11 (1.0%)
Night sweats	1 (0.4%)	6 (1.5%)	4 (1.0%)	1 (0.3%)	11 (1.0%)
Urticaria	2 (0.8%)	4 (1.0%)	5 (1.2%)	0	9 (0.8%)
Psoriasis	0	1 (0.3%)	5 (1.2%)	2 (0.6%)	8 (0.7%)
Hyperhidrosis	0	2 (0.5%)	5 (1.2%)	0	7 (0.6%)
Skin lesion	2 (0.8%)	2 (0.5%)	3 (0.7%)	2 (0.6%)	7 (0.6%)
Dermatitis contact	0	3 (0.8%)	3 (0.7%)	0	6 (0.5%)
Dry skin	0	1 (0.3%)	5 (1.2%)	0	6 (0.5%)
Rash pruritic	1 (0.4%)	4 (1.0%)	2 (0.5%)	0	6 (0.5%)
Dermal cyst	1 (0.4%)	0	4 (1.0%)	1 (0.3%)	5 (0.4%)
Erythema	1 (0.4%)	3 (0.8%)	2 (0.5%)	0	5 (0.4%)
General disorders and administration site conditions	46 (19.0%)	80 (20.2%)	84 (20.0%)	31 (9.1%)	195 (16.9%)
Nervous system disorders	39 (16.1%)	69 (17.4%)	79 (18.9%)	30 (8.8%)	178 (15.4%)
Respiratory, thoracic and mediastinal disorders	27 (11.2%)	44 (11.1%)	68 (16.2%)	23 (6.7%)	135 (11.7%)
Cough	9 (3.7%)	13 (3.3%)	29 (6.9%)	6 (1.8%)	48 (4.1%)
Oropharyngeal pain	5 (2.1%)	11 (2.8%)	16 (3.8%)	5 (1.5%)	32 (2.8%)
Nasal congestion	9 (3.7%)	5 (1.3%)	8 (1.9%)	3 (0.9%)	16 (1.4%)
Rhinorrhoea	4 (1.7%)	3 (0.8%)	7 (1.7%)	2 (0.6%)	12 (1.0%)
Sinus congestion	3 (1.2%)	5 (1.3%)	4 (1.0%)	1 (0.3%)	10 (0.9%)
Dyspnoea	0	1 (0.3%)	3 (0.7%)	4 (1.2%)	8 (0.7%)
Asthma	0	1 (0.3%)	4 (1.0%)	2 (0.6%)	7 (0.6%)

Injury, poisoning and procedural complications	20 (8.3%)	22 (5.6%)	53 (12.6%)	12 (3.5%)	87 (7.5%)
Investigations	19 (7.9%)	33 (8.3%)	26 (6.2%)	17 (5.0%)	76 (6.6%)
Psychiatric disorders	6 (2.5%)	25 (6.3%)	30 (7.2%)	11 (3.2%)	66 (5.7%)
Metabolism and nutrition disorders	12 (5.0%)	17 (4.3%)	31 (7.4%)	14 (4.1%)	62 (5.4%)
Blood and lymphatic system disorders	10 (4.1%)	20 (5.1%)	27 (6.4%)	13 (3.8%)	60 (5.2%)
Eye disorders	13 (5.4%)	18 (4.5%)	25 (6.0%)	8 (2.3%)	51 (4.4%)
Vascular disorders	4 (1.7%)	11 (2.8%)	20 (4.8%)	6 (1.8%)	37 (3.2%)
Hypertension	1 (0.4%)	4 (1.0%)	4 (1.0%)	2 (0.6%)	10 (0.9%)
Deep vein thrombosis	0	2 (0.5%)	5 (1.2%)	0	7 (0.6%)
Hot flush	1 (0.4%)	2 (0.5%)	4 (1.0%)	1 (0.3%)	7 (0.6%)
Renal and urinary disorders	6 (2.5%)	12 (3.0%)	17 (4.1%)	6 (1.8%)	35 (3.0%)
Reproductive system and breast disorders	12 (5.0%)	7 (1.8%)	19 (4.5%)	3 (0.9%)	29 (2.5%)
Cardiac disorders	2 (0.8%)	3 (0.8%)	11 (2.6%)	6 (1.8%)	20 (1.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (2.9%)	5 (1.3%)	13 (3.1%)	1 (0.3%)	19 (1.6%)
Ear and labyrinth disorders	4 (1.7%)	2 (0.5%)	14 (3.3%)	3 (0.9%)	19 (1.6%)
Immune system disorders	5 (2.1%)	5 (1.3%)	9 (2.1%)	3 (0.9%)	17 (1.5%)

Infections, skin disorders (rash and itch), respiratory disorders (cough), vascular disorders (DVT), procedural complications and psychiatric disorders (depression) are more commonly associated with study drug. For vascular disorders where 7 subjects exposed to Stelara are recorded with venous thrombosis versus 0 for placebo exposure.

The company carried out a re-evaluation of cases of thrombosis after day 120 of the current procedure. 2 subjects were re-classified resulting in 8 subjects with thrombosis in the Stelara group and 1 subject with thrombosis in the placebo group (table 30):

Table 30 Number of subjects with 1 or more treatment-emergent deep vein thrombosis or thrombosis adverse events through Week 44 by MedDRA system-organ class and preferred term; treated subjects

		Ustekinumab			
			Nonresponders to IV induction dosing		
	Placebo SC[a]	Responders to ustekinumab IV induction dosing[b]	Subsequent responders at Week 8 of maintenance → continue ustekinumab SC[c]	Subsequent non-responders at Week 8 of maintenance → discontinue at Week 8[d]	All ustekinumab
Analysis set: Treated subjects	242	396	419	342	1157
Avg duration of follow-up (weeks)	34.0	30.0	41.9	18.7	30.9
Total subject-years of follow-up	158.0	258.2	337.3	122.6	718.1
System-organ class/preferred term					
Vascular disorders	4 (1.7%)	11 (2.8%)	20 (4.8%)	6 (1.8%)	37 (3.2%)
Deep vein thrombosis	0	2 (0.5%)	5 (1.2%)	0	7 (0.6%)
Thrombosis	1 (0.4%)	0	1 (0.2%)	0	1 (0.1%)

[a] Includes all data for subjects who were in clinical response to placebo IV induction dosing and received placebo SC in this maintenance study, and the data from Week 8 onward for subjects who were in clinical response to ustekinumab IV induction dosing and received placebo SC in this maintenance study.
[b] Includes all data for subjects who were in clinical response to ustekinumab IV induction dosing and received ustekinumab SC (q8w or q12w, with or without dose adjustment) in this maintenance study, and data from Week 0 to Week 8 for subjects who were in clinical response to ustekinumab IV induction dosing and received placebo SC in this maintenance study
[c] Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q12w. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q8w.
[d] Subjects who received ustekinumab 130 mg IV at Week 0 and discontinued at Week 8. Subjects who received ustekinumab 90 mg SC at Week 0 and discontinued at Week 8.

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The total number of subjects in each group (placebo and Stelara) are small in terms of the detection of harm and so it is not apparent that detailed statistical analysis is helpful. On simple examination of table 31, however, the event rate of DVT per 100 person years in the 'all-Stelara group' is about twice that of the placebo group i.e. 1.25 *v*. 0.63, as shown in table 31:

Table 31 Number of treatment-emergent thrombosis events per hundred subject-years of follow-up from maintenance Week 0 through Week 44; Treated subjects in CNTO1275CRD3003

		Ustekinumab			
			Non-responders to IV induction dosing		
	Placebo [a]	Responders to ustekinumab IV induction dosing[b]	Subsequent responders at Week 8 of maintenance → continue ustekinumab SC[c]	Subsequent non-responders at Week 8 of maintenance → discontinue at Week 8[d]	All ustekinumab
Analysis set: Treated subjects in CNTO1275CRD3003	242	396	419	342	1157
Avg duration of follow-up (weeks)	34.0	30.0	41.9	18.7	30.9
Total subject-years of follow-up	158.0	258.2	337.3	122.6	718.1
System-organ class/preferred term					
Vascular disorders					
Deep vein thrombosis					
Event rate per 100 subject-years	0.00	0.77	1.78	0.00	1.11
95% Confidence Interval[e]	(0.00, 1.90)	(0.09, 2.80)	(0.65, 3.87)	(0.00, 2.44)	(0.48, 2.20)
Thrombosis					
Event rate per 100 subject-years	0.63	0.00	0.30	0.00	0.14
95% Confidence Interval[e]	(0.02, 3.53)	(0.00, 1.16)	(0.01, 1.65)	(0.00, 2.44)	(0.00, 0.78)
Deep vein thrombosis and Thrombosis					
Event rate per 100 subject-years	0.63	0.77	2.08	0.00	1.25
95% Confidence Interval[e]	(0.02, 3.53)	(0.09, 2.80)	(0.83, 4.28)	(0.00, 2.44)	(0.57, 2.38)

[a] Includes all data for subjects who were in clinical response to placebo IV induction dosing and received placebo SC in this maintenance study, and the data from Week 8 onward for subjects who were in clinical response to ustekinumab IV induction dosing and received placebo SC in this maintenance study.
[b] Includes all data for subjects who were in clinical response to ustekinumab IV induction dosing and received ustekinumab SC (q8w or q12w, with or without dose adjustment) in this maintenance study, and data from Week 0 to Week 8 for subjects who were in clinical response to ustekinumab IV induction dosing and received placebo SC in this maintenance study
[c] Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q12w. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q8w.
[d] Subjects who received ustekinumab 130 mg IV at Week 0 and discontinued at Week 8. Subjects who received ustekinumab 90 mg SC at Week 0 and discontinued at Week 8.
[e] Confidence intervals based on an exact method assuming that the observed number of events follows a Poisson distribution.

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Adverse events of interest

By the primary analysis of pooled phase 3 data, the company did not find difference between study drug and placebo with regards to infection or infection requiring antibiotics.

There was one event of presumed tuberculosis who was treated empirically.

4 subjects (2 placebo-treated subjects and 2 ustekinumab-treated subjects) experienced AEs suggestive of a possible infusion reaction. All of the events identified in these subjects were assessed as mild or moderate severity, with the exception of severe dysponea reported in a subject that received a placebo infusion. The events were self-limited in all cases and required no intervention other than oral antihistamine.

1.7% of subjects reported a placebo injection-site reaction and 3.0% reported an ustekinumab injection-site reaction. No serious injection-site reactions or injection-site reactions of severe intensity were reported.

There were no possible anaphylactic reactions or possible serum sickness-like reactions in ustekinumab-treated subjects through approximately 1 year of treatment in the Crohn's disease studies combined.

In the combined Crohn's disease studies, through approximately 1 year of treatment, for all malignancies, the incidence of malignancies per 100 subject-years of follow-up was comparable between placebo-treated subjects and ustekinumab-treated subjects (0.58 [95% CI:0.07, 2.09] in the placebo group and 0.63 [95% CI: 0.25, 1.31] in the combined ustekinumab group).

MACE: through approximately 1 year of treatment, in the combined Crohn's disease studies, there was 1 event of a subarachnoid hemorrhage due to aneurysm rupture which was adjudicated as a non-fatal stroke in a non-responder to ustekinumab induction who subsequently received ustekinumab 90 SC q8w as maintenance treatment in study CRD3003. Overall, up to 1 year, there is no consistent evidence that ustekinumab increases cardiovascular risk.

There were no events of reversible posterior leukoencephalopathy reported.

Summary of Safety for Crohn's Disease Pooled with Psoriasis and PsA

A summary of key safety events from the Crohn's disease studies compared with the pooled indications of Crohn's disease, psoriasis, and PsA, through approximately 1 year of follow-up, is shown in Table 3:

Key Safety Events for Crohn's Disease Pooled with Psoriasis and PsA: Through 1 Year

Table 3: Summary of key safety events per hundred subject-years of follow up through one year of follow up; treated subjects in Psoriasis, PsA, and Crohn's disease studies[a]

	Psoriasis		PsA		Crohn's		All Diseases Pooled	
	Placebo[b]	Ustekinumab[c]	Placebo[d]	Ustekinumab[e]	Placebo[f]	Ustekinumab[g]	Placebo	Ustekinumab
Subjects treated	733	3117	379	1018	943	1749	2055	5884
Avg duration of follow-up (weeks)	12.93	42.80	19.90	43.40	19.12	32.89	17.05	39.96
Avg duration of treatment (weeks)[h]	4.90	26.49	11.96	27.66	9.87	18.80	8.41	24.41
Subjects who discontinued study agent because of adverse events	17 (2.3%)	86 (2.8%)	22 (5.8%)	31 (3.0%)	45 (4.8%)	108 (6.2%)	84 (4.1%)	225 (3.8%)
Total subject-years of follow-up	182	2566	145	850	347	1106	674	4521
Event rate per 100 subject-years								
AEs	414.81	390.60	343.41	254.24	712.16	641.63	552.41	426.39
SAEs	8.78	8.77	13.79	9.30	43.84	35.35	27.89	15.37
Infections[i]	120.71	137.40	102.75	78.04	145.09	133.98	129.38	125.41
Serious Infections[i]	1.65	1.40	0.69	0.94	6.92	6.42	4.15	2.54
Adjudicated serious MACE	0.55	0.55	0.69	0.71	0.00	0.09	0.30	0.46
Deaths	0.00	0.19	0.00	0.00	0.00	0.00	0.00	0.11
Malignancies (excluding NMSC)	0.55	0.43	0.00	0.12	0.00	0.36	0.15	0.35

AE=adverse event; MACE=major cardiovascular event; NMSC=nonmelanoma skin cancer; PsA=psoriatic arthritis; SAE=serious adverse event

[a] Crohn's: C0379T07(only placebo-controlled IV population in population 1; through Week 28), C0743T26 (through Week 36), CNTO1275CRD3001 (through Week 8 for subjects who entered CNTO1275CRD3003; through Week 20 for subjects who did not enter CNTO1275CRD3003), CNTO1275CRD3002 (through Week 8 for subjects who entered CNTO1275CRD3003; through Week 20 for subjects who did not enter CNTO1275CRD3003), CNTO1275CRD3003 (through Week 44); Psoriasis: C0379T04 (through Week 52), C0743T08 (through Week 52), C0743T09 (through Week 52), C0743T12 (through Week 52); PsA: C0743T10 (through Week 36), CNTO1275PSA3001 (through Week 52), CNTO1275PSA3002 (through Week 60).

[b] Includes data up to the time of crossover.

[c] Includes data from the first ustekinumab dose onward for subjects who crossed over from placebo.

[d] Includes data up to the time of early escape or crossover.

[e] Includes data from the first ustekinumab dose onward for subjects who early escaped or crossed over from placebo.

[f] Includes data up to the first ustekinumab dose for subjects who were initially treated with placebo; includes data on or after 16 weeks from the first ustekinumab dose for subjects who were initially treated with ustekinumab and were crossed over or rerandomized to placebo.

[g] Includes data up to 16 weeks from the first ustekinumab dose for subjects who were crossed over or rerandomized to placebo.

[h] Total number of IV and SC administrations.

[i] Infection as assessed by the investigator.

[TSFKEY81A.RTF] [CNTO1275\Z_SCS\DBR_2015_07\RE_2015_07\PROD\TSFKEY81A.SAS] 13OCT2015, 11:14

Overall the safety data from the Crohn's disease studies did not appear to have altered the safety profile of ustekinumab established in the approved indications of psoriasis and PsA

Serious adverse event/deaths/other significant events

Deaths

Through approximately 1 year of treatment, there were no deaths in the combined Crohn's disease studies.

The company is aware of 5 deaths that occurred during the ongoing extension for CRD3003. The causes of death (3 presumed cardiovascular, 1 renal, and 1 suicide) are not atypical of an IBD population and a concerning pattern of events was not seen.

Serious adverse events, Induction phase

Pooled Data from Phase 3 Studies:

Serious adverse events occurred at 6.0% in the placebo group, 4.9% in the ustekinumab 130 mg IV group, and 5.3% in the ustekinumab ~6 mg/kg IV group with no evidence of a dose effect.

The SOC with the highest proportions of SAEs that occurred in subjects in the combined ustekinumab group were Gastrointestinal Disorders (3.9% in the placebo group and 2.7% in the combined ustekinumab group). Infections and Infestations was the SOC that was next highest: 1.1% in the placebo group and 1.4% in the combined ustekinumab group.

Results are shown in the following table:

TSFSAE01A: Number of subjects with 1 or more treatment-emergent serious adverse events during placebo-controlled induction (Week 0 to Week 8) by MedDRA system-organ class and preferred term; treated subjects in Phase 3 Crohn's disease studies (CNTO1275CRD3001 and CNTO1275CRD3002)

		Ustekinumab		
	Placebo	130 mg	6 mg/kg	Combined
Subjects treated	466	471	470	941
Avg duration of follow-up (weeks)	8.18	8.22	8.16	8.19
Avg exposure (number of administrations)	1.00	1.00	1.00	1.00
Total number of subjects with serious adverse events	28 (6.0%)	23 (4.9%)	25 (5.3%)	48 (5.1%)
System-organ class/preferred term				
Gastrointestinal disorders	18 (3.9%)	12 (2.5%)	13 (2.8%)	25 (2.7%)
Crohn's disease	13 (2.8%)	12 (2.5%)	7 (1.5%)	19 (2.0%)
Small intestinal obstruction	1 (0.2%)	1 (0.2%)	3 (0.6%)	4 (0.4%)
Abdominal pain	0	0	1 (0.2%)	1 (0.1%)
Colitis	0	0	1 (0.2%)	1 (0.1%)
Colonic fistula	0	0	1 (0.2%)	1 (0.1%)
Diarrhoea	2 (0.4%)	1 (0.2%)	0	1 (0.1%)
Gastric ulcer haemorrhage	0	0	1 (0.2%)	1 (0.1%)
Intestinal obstruction	1 (0.2%)	0	0	0
Large intestine perforation	1 (0.2%)	0	0	0
Small intestinal perforation	1 (0.2%)	0	0	0
Infections and infestations	5 (1.1%)	6 (1.3%)	7 (1.5%)	13 (1.4%)
Abscess intestinal	0	1 (0.2%)	1 (0.2%)	2 (0.2%)
Anal abscess	2 (0.4%)	2 (0.4%)	0	2 (0.2%)
Clostridium difficile infection	0	0	1 (0.2%)	1 (0.1%)
Escherichia sepsis	0	0	1 (0.2%)	1 (0.1%)
Gastroenteritis	0	0	1 (0.2%)	1 (0.1%)
Gastroenteritis viral	0	1 (0.2%)	0	1 (0.1%)
Intervertebral discitis	0	0	1 (0.2%)	1 (0.1%)
Meningitis listeria	0	0	1 (0.2%)	1 (0.1%)
Pelvic abscess	0	1 (0.2%)	0	1 (0.1%)
Perineal abscess	0	0	1 (0.2%)	1 (0.1%)
Peritonitis	0	0	1 (0.2%)	1 (0.1%)
Vulval abscess	0	1 (0.2%)	0	1 (0.1%)
Infected fistula	1 (0.2%)	0	0	0
Pneumonia	1 (0.2%)	0	0	0

TSFSAE01A: Number of subjects with 1 or more treatment-emergent serious adverse events during placebo-controlled induction (Week 0 to Week 8) by MedDRA system-organ class and preferred term; treated subjects in Phase 3 Crohn's disease studies (CNTO1275CRD3001 and CNTO1275CRD3002)

		Ustekinumab		
	Placebo	130 mg	6 mg/kg	Combined
Pneumonia viral	1 (0.2%)	0	0	0
General disorders and administration site conditions	1 (0.2%)	2 (0.4%)	0	2 (0.2%)
Impaired healing	0	1 (0.2%)	0	1 (0.1%)
Non-cardiac chest pain	0	1 (0.2%)	0	1 (0.1%)
Pyrexia	1 (0.2%)	0	0	0
Injury, poisoning and procedural complications	0	1 (0.2%)	1 (0.2%)	2 (0.2%)
Incisional hernia	0	1 (0.2%)	0	1 (0.1%)
Road traffic accident	0	0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders	2 (0.4%)	2 (0.4%)	0	2 (0.2%)
Dehydration	0	1 (0.2%)	0	1 (0.1%)
Hypocalcaemia	0	1 (0.2%)	0	1 (0.1%)
Hypokalaemia	1 (0.2%)	1 (0.2%)	0	1 (0.1%)
Hypomagnesaemia	0	1 (0.2%)	0	1 (0.1%)
Malnutrition	1 (0.2%)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.2%)	1 (0.2%)	2 (0.2%)
Pneumothorax spontaneous	0	1 (0.2%)	1 (0.2%)	2 (0.2%)
Vascular disorders	0	1 (0.2%)	1 (0.2%)	2 (0.2%)
Lymphocele	0	0	1 (0.2%)	1 (0.1%)
Phlebitis superficial	0	1 (0.2%)	0	1 (0.1%)
Blood and lymphatic system disorders	2 (0.4%)	1 (0.2%)	0	1 (0.1%)
Anaemia	1 (0.2%)	1 (0.2%)	0	1 (0.1%)
Pancytopenia	1 (0.2%)	0	0	0
Cardiac disorders	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
Atrial fibrillation	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
Cardiac failure	0	0	1 (0.2%)	1 (0.1%)
Hepatobiliary disorders	1 (0.2%)	0	1 (0.2%)	1 (0.1%)
Cholangitis	0	0	1 (0.2%)	1 (0.1%)
Bile duct stone	1 (0.2%)	0	0	0
Immune system disorders	0	0	1 (0.2%)	1 (0.1%)
Hypersensitivity	0	0	1 (0.2%)	1 (0.1%)
Renal and urinary disorders	0	1 (0.2%)	0	1 (0.1%)
Nephrolithiasis	0	1 (0.2%)	0	1 (0.1%)
Reproductive system and breast disorders	1 (0.2%)	0	1 (0.2%)	1 (0.1%)

TSFSAE01A: Number of subjects with 1 or more treatment-emergent serious adverse events during placebo-controlled induction (Week 0 to Week 8) by MedDRA system-organ class and preferred term; treated subjects in Phase 3 Crohn's disease studies (CNTO1275CRD3001 and CNTO1275CRD3002)

		Ustekinumab		
	Placebo	130 mg	6 mg/kg	Combined
Female genital tract fistula	0	0	1 (0.2%)	1 (0.1%)
Dysmenorrhoea	1 (0.2%)	0	0	0

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Pooled Data from Phase 2 and Phase 3 Studies

Results were consistent with those of the pooled phase 3 data.

Serious adverse events, maintenance phase

Data from Phase 3 Study

During the maintenance phase (up to the point of dose adjustment) in study CRD3003, the proportions of randomized subjects with SAEs were comparable between treatment groups with no evidence of a dose effect (15.0% in the placebo group, 12.1% in the ustekinumab 90 mg SC q12w group, and 9.9% in the ustekinumab 90 mg SC q8w group).

Results are shown in the following table:

TSFAE04A: Number of subjects with 1 or more serious adverse events through Week 44 or up to the time of dose adjustment by MedDRA system-organ class and preferred term; treated subjects who were randomized

	placebo SC[a,b]	ustekinumab[b] 90 mg SC q12w	ustekinumab[b] 90 mg SC q8w	Combined
Analysis set: Treated subjects who were randomized	133	132	131	263
Avg duration of follow-up (weeks)	32.0	36.6	35.2	35.9
Total number of subjects with 1 or more treatment-emergent serious adverse events	20 (15.0%)	16 (12.1%)	13 (9.9%)	29 (11.0%)
System-organ class/preferred term				
Gastrointestinal disorders	11 (8.3%)	6 (4.5%)	8 (6.1%)	14 (5.3%)
Crohn's disease	7 (5.3%)	5 (3.8%)	4 (3.1%)	9 (3.4%)
Large intestinal stenosis	0	0	2 (1.5%)	2 (0.8%)
Small intestinal obstruction	0	1 (0.8%)	1 (0.8%)	2 (0.8%)
Abdominal pain	0	0	1 (0.8%)	1 (0.4%)
Large intestinal obstruction	0	0	1 (0.8%)	1 (0.4%)
Anal fistula	2 (1.5%)	0	0	0
Enterovesical fistula	1 (0.8%)	0	0	0
Large intestine perforation	1 (0.8%)	0	0	0
Infections and infestations	3 (2.3%)	7 (5.3%)	3 (2.3%)	10 (3.8%)
Appendicitis	0	2 (1.5%)	0	2 (0.8%)
Abdominal infection	0	1 (0.8%)	0	1 (0.4%)
Anal abscess	1 (0.8%)	1 (0.8%)	0	1 (0.4%)
Bacteraemia	0	1 (0.8%)	0	1 (0.4%)
Campylobacter gastroenteritis	0	1 (0.8%)	0	1 (0.4%)
Gastroenteritis	0	1 (0.8%)	0	1 (0.4%)
Gastroenteritis viral	0	1 (0.8%)	0	1 (0.4%)
Ophthalmic herpes zoster	0	0	1 (0.8%)	1 (0.4%)
Pneumonia	2 (1.5%)	0	1 (0.8%)	1 (0.4%)
Postoperative wound infection	0	1 (0.8%)	0	1 (0.4%)
Viral infection	0	0	1 (0.8%)	1 (0.4%)
Vascular disorders	0	2 (1.5%)	0	2 (0.8%)
Deep vein thrombosis	0	1 (0.8%)	0	1 (0.4%)
Essential hypertension	0	1 (0.8%)	0	1 (0.4%)
Injury, poisoning and procedural complications	0	1 (0.8%)	0	1 (0.4%)
Allergic transfusion reaction	0	1 (0.8%)	0	1 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8%)	0	1 (0.8%)	1 (0.4%)
Ovarian adenoma	0	0	1 (0.8%)	1 (0.4%)
Meningioma	1 (0.8%)	0	0	0
Nervous system disorders	1 (0.8%)	0	1 (0.8%)	1 (0.4%)
Migraine	0	0	1 (0.8%)	1 (0.4%)
Headache	1 (0.8%)	0	0	0
Psychiatric disorders	0	1 (0.8%)	0	1 (0.4%)
Suicidal ideation	0	1 (0.8%)	0	1 (0.4%)
Musculoskeletal and connective tissue disorders	3 (2.3%)	0	0	0
Arthralgia	1 (0.8%)	0	0	0
Fibromyalgia	1 (0.8%)	0	0	0
Lumbar spinal stenosis	1 (0.8%)	0	0	0
Social circumstances	1 (0.8%)	0	0	0
Substance abuser	1 (0.8%)	0	0	0

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Includes data up to the time of dose adjustment (i.e., time of meeting loss of response criteria).

[TSFAE04A.rtf] [CNTO1275\CRD3003\DBR_CSR\RE_CSR\tsfae04a.sas] 07OCT2015, 17:59

Results are consistent with events described in the SPC.

Pooled Data from Phase 2 and Phase 3 Studies

Results were consistent with those of the pooled phase 3 data.

The company also presents supportive analysis for all subjects treated in maintenance study CRD3003: events per 100 subject-years and proportions of subjects with events. These presentations provide data for all subjects treated within maintenance study CRD3003, both randomized and nonrandomized subjects. The table below shows data for events per 100 subject years:

TSFAE04E: Number of serious adverse events per hundred subject-years of follow-up through Week 44 by MedDRA system-organ class and preferred term; treated subjects

			ustekinumab		
	placebo SC[a]	Responders to ustekinumab IV induction dosing[b]	Non-responders to IV induction dosing: Subsequent responders at Week 8 of maintenance → continue ustekinumab SC[c]	Non-responders to IV induction dosing: Subsequent non-responders at Week 8 of maintenance → discontinue at Week 8[d]	All ustekinumab
Analysis set: Treated subjects	242	396	419	342	1157
Avg duration of follow-up (weeks)	34.0	30.0	41.9	18.7	30.9
Total subject-years of follow-up	158.0	258.2	337.3	122.6	718.1
Number of treatment-emergent serious adverse events per hundred subject-years of follow-up	24.05	23.63	27.57	47.31	29.52
System-organ class/preferred term					
Gastrointestinal disorders	12.03	13.17	13.34	29.36	16.01
Crohn's disease	6.96	9.30	5.63	22.02	9.75
Small intestinal obstruction	0.63	1.55	3.56	2.45	2.65
Abdominal pain	0	0.39	0.59	0	0.42
Intestinal obstruction	0	0	0.89	0	0.42
Anal fistula	1.27	0	0.59	0	0.28
Faecaloma	0	0	0.59	0	0.28
Intestinal stenosis	0	0	0.30	0.82	0.28
Large intestinal obstruction	0	0.39	0	0.82	0.28
Large intestinal stenosis	0	0.77	0	0	0.28
Abdominal adhesions	0	0	0	0.82	0.14
Abdominal discomfort	0	0	0.30	0	0.14
Abdominal hernia	0	0.39	0	0	0.14
Colitis	0	0	0.30	0	0.14
Cyclic vomiting syndrome	0	0	0.30	0	0.14
Diarrhoea	0	0	0	0.82	0.14
Enterocutaneous fistula	0	0	0	0.82	0.14
Faecal volume increased	0	0	0.30	0	0.14
Gastrointestinal haemorrhage	0	0.39	0	0	0.14
Small intestinal stenosis	0	0	0	0.82	0.14
Anal fissure	0.63	0	0	0	0
Constipation	0.63	0	0	0	0
Enterovesical fistula	0.63	0	0	0	0
Large intestine perforation	0.63	0	0	0	0
Mallory-Weiss syndrome	0.63	0	0	0	0
Infections and infestations	3.16	6.20	4.74	5.71	5.43
Anal abscess	1.27	0.39	0.89	1.63	0.84
Gastroenteritis	0	0.39	0.30	0.82	0.42
Abdominal abscess	0	0	0.30	0.82	0.28
Appendicitis	0	0.77	0	0	0.28
Bacteraemia	0	0.39	0.30	0	0.28
Gastroenteritis viral	0	0.39	0.30	0	0.28
Perirectal abscess	0	0	0.59	0	0.28
Pneumonia	1.27	0.39	0.30	0	0.28
Viral infection	0	0.39	0	0.82	0.28
Abdominal infection	0	0.39	0	0	0.14
Acute sinusitis	0	0	0.30	0	0.14
Bronchitis	0	0	0.30	0	0.14
Campylobacter gastroenteritis	0	0.39	0	0	0.14
Clostridium difficile colitis	0.63	0	0	0.82	0.14
Device related infection	0	0	0	0.82	0.14
Hepatitis infectious mononucleosis	0	0	0.30	0	0.14

TSFAE04E: Number of serious adverse events per hundred subject-years of follow-up through Week 44 by MedDRA system-organ class and preferred term; treated subjects

			ustekinumab		
			Non-responders to IV induction dosing		
	placebo SC[a]	Responders to ustekinumab IV induction dosing[b]	Subsequent responders at Week 8 of maintenance → continue ustekinumab SC[c]	Subsequent non-responders at Week 8 of maintenance → discontinue at Week 8[d]	All ustekinumab
Influenza	0	0.39	0	0	0.14
Lobar pneumonia	0	0.39	0	0	0.14
Ophthalmic herpes zoster	0	0.39	0	0	0.14
Peritonitis	0	0.39	0	0	0.14
Pneumonia pneumococcal	0	0.39	0	0	0.14
Pneumonia staphylococcal	0	0	0.30	0	0.14
Postoperative wound infection	0	0.39	0	0	0.14
Rectal abscess	0	0	0.30	0	0.14
Sepsis	0	0	0.30	0	0.14
Injury, poisoning and procedural complications	0.63	0.39	2.37	0	1.25
Ligament sprain	0	0	0.59	0	0.28
Alcohol poisoning	0	0	0.30	0	0.14
Allergic transfusion reaction	0	0.39	0	0	0.14
Contusion	0	0	0.30	0	0.14
Heat stroke	0	0	0.30	0	0.14
Humerus fracture	0	0	0.30	0	0.14
Procedural pain	0	0	0.30	0	0.14
Sternal injury	0	0	0.30	0	0.14
Anastomotic haemorrhage	0.63	0	0	0	0
General disorders and administration site conditions	0	0.39	1.19	1.63	0.97
Non-cardiac chest pain	0	0	0.59	0	0.28
Pyrexia	0	0	0.59	0	0.28
Asthenia	0	0.39	0	0	0.14
Dysplasia	0	0	0	0.82	0.14
Oedema peripheral	0	0	0	0.82	0.14
Musculoskeletal and connective tissue disorders	2.53	0.39	1.48	0.82	0.97
Arthralgia	0.63	0	0.30	0	0.14
Back pain	0	0	0.30	0	0.14
Costochondritis	0	0	0.30	0	0.14
Polyarthritis	0	0	0	0.82	0.14
Rotator cuff syndrome	0.63	0.39	0	0	0.14
Spinal column stenosis	0	0	0.30	0	0.14
Spinal osteoarthritis	0	0	0.30	0	0.14
Fibromyalgia	0.63	0	0	0	0
Lumbar spinal stenosis	0.63	0	0	0	0
Nervous system disorders	0.63	0.39	0	3.26	0.70
Convulsion	0	0	0	0.82	0.14
Migraine	0	0.39	0	0	0.14
Radiculopathy	0	0	0	0.82	0.14
Subarachnoid haemorrhage	0	0	0	0.82	0.14
Syncope	0	0	0	0.82	0.14
Headache	0.63	0	0	0	0
Psychiatric disorders	0	0.77	0.59	0.82	0.70
Depression	0	0.39	0.30	0.82	0.42
Hallucination	0	0	0.30	0	0.14
Suicidal ideation	0	0.39	0	0	0.14
Renal and urinary disorders	0	0.39	0.59	1.63	0.70
Nephrolithiasis	0	0.39	0.30	0	0.28
Calculus ureteric	0	0	0	0.82	0.14
Renal colic	0	0	0.30	0	0.14
Renal tubular necrosis	0	0	0	0.82	0.14
Vascular disorders	0	0.77	0.89	0	0.70

TSFAE04E: Number of serious adverse events per hundred subject-years of follow-up through Week 44 by MedDRA system-organ class and preferred term; treated subjects

			ustekinumab		
			Non-responders to IV induction dosing		
	placebo SC[a]	Responders to ustekinumab IV induction dosing[b]	Subsequent responders at Week 8 of maintenance → continue ustekinumab SC[c]	Subsequent non-responders at Week 8 of maintenance → discontinue at Week 8[d]	All ustekinumab
Deep vein thrombosis	0	0.39	0.89	0	0.56
Essential hypertension	0	0.39	0	0	0.14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1.27	0.39	0.59	0	0.42
Ovarian adenoma	0	0.39	0	0	0.14
Small intestine adenocarcinoma	0	0	0.30	0	0.14
Uterine leiomyoma	0	0	0.30	0	0.14
Fibroadenoma of breast	0.63	0	0	0	0
Meningioma	0.63	0	0	0	0
Blood and lymphatic system disorders	0	0	0.30	0.82	0.28
Anaemia	0	0	0	0.82	0.14
Iron deficiency anaemia	0	0	0.30	0	0.14
Cardiac disorders	0	0	0.30	0.82	0.28
Atrial fibrillation	0	0	0	0.82	0.14
Cardiomyopathy	0	0	0.30	0	0.14
Hepatobiliary disorders	0.63	0.39	0	0.82	0.28
Cholecystitis	0.63	0.39	0	0.82	0.28
Investigations	0	0	0	1.63	0.28
Blood electrolytes abnormal	0	0	0	0.82	0.14
Hepatic enzyme increased	0	0	0	0.82	0.14
Metabolism and nutrition disorders	0	0	0.59	0	0.28
Malnutrition	0	0	0.59	0	0.28
Reproductive system and breast disorders	0.63	0	0.59	0	0.28
Bartholin's cyst	0	0	0.30	0	0.14
Uterine prolapse	0	0	0.30	0	0.14
Female genital tract fistula	0.63	0	0	0	0
Pregnancy, puerperium and perinatal conditions	0.63	0	0	0	0
Abortion spontaneous	0.63	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0.63	0	0	0	0
Nasal polyps	0.63	0	0	0	0
Social circumstances	1.27	0	0	0	0
Breast prosthesis user	0.63	0	0	0	0
Substance abuser	0.63	0	0	0	0

[a] Includes all data for subjects who were in clinical response to placebo IV induction dosing and received placebo SC in this maintenance study, and the data from Week 8 onward for subjects who were in clinical response to ustekinumab IV induction dosing and received placebo SC in this maintenance study.
[b] Includes data up to Week 8 for subjects who were in clinical response to ustekinumab IV induction dosing and received placebo SC in this maintenance study, and all data for subjects who were in clinical response to ustekinumab IV induction dosing and received ustekinumab SC (q8w or q12w, with or without dose adjustment) in this maintenance study.
[c] Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q12w. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q8w.
[d] Subjects who received ustekinumab 130 mg IV at Week 0 and discontinued at Week 8. Subjects who received ustekinumab 90 mg SC at Week 0 and discontinued at Week 8.

[TSFAE04E.rtf] [CNTO1275\CRD3003\DBR_CSR\RE_CSR\tsfae04e.sas] 07OCT2015, 17:

Consistent with previous analyses, the SOCs with the highest proportions of SAEs were Gastrointestinal Disorders and Infections and Infestations and overall, the most frequently reported SAEs in both supportive analyses were Crohn's disease, small intestinal obstruction, anal abscess, gastroenteritis, depression and deep vein thrombosis.

Infections / infestations, procedural complications, administration site conditions, psychiatric disorders (depression) and vascular disorders (DVT) were apparently more common in those exposed to study drug during the time period described by the above table.
It is noted in the above table that the number gastro-intestinal events was similar in the study drug and placebo groups.

4 subjects exposed to study drug developed a DVT versus none on placebo during the maintenance period, table TSFSE04F submitted by the company, as shown in the extract below:

TSFAE04F: Number of subjects with 1 or more serious adverse events through Week 44 by MedDRA system-organ class and preferred term; treated subjects

		ustekinumab			
			Non-responders to IV induction dosing		
	placebo SC[a]	Responders to ustekinumab IV induction dosing[b]	Subsequent responders at Week 8 of maintenance → continue ustekinumab SC[c]	Subsequent non-responders at Week 8 of maintenance → discontinue at Week 8[d]	All ustekinumab
Analysis set: Treated subjects	242	396	419	342	1157
Avg duration of follow-up (weeks)	34.0	30.0	41.9	18.7	30.9
Total number of subjects with 1 or more treatment-emergent serious adverse events	37 (15.3%)	47 (11.9%)	73 (17.4%)	50 (14.6%)	170 (14.7%)
System-organ class/preferred term					
Vascular disorders	0	2 (0.5%)	3 (0.7%)	0	5 (0.4%)
Deep vein thrombosis	0	1 (0.3%)	3 (0.7%)	0	4 (0.3%)
Essential hypertension	0	1 (0.3%)	0	0	1 (0.1%)

Laboratory findings

For both induction and maintenance phases, changes in laboratory findings were not considered to be clinically significant.

Q8W dosing versus Q12W dosing

The overall proportions of subjects with AEs were comparable between treatment groups with no evidence of a dose effect between the 2 ustekinumab dose groups (83.5% in the placebo group, 80.3% in the ustekinumab 90 mg SC q12w group, and 81.7% in the ustekinumab 90 mg SC q8w group) as shown in the extract of the following table:

TSFAE01A: Number of subjects with 1 or more treatment-emergent adverse events through Week 44 or up to the time of dose adjustment by MedDRA system-organ class and preferred term; treated subjects who were randomized

	placebo SC[a,b]	ustekinumab[b] 90 mg SC q12w	ustekinumab[b] 90 mg SC q8w	Combined
Analysis set: Treated subjects who were randomized	133	132	131	263
Average duration of follow-up (Weeks)	32.0	36.6	35.2	35.9
Total number of subjects with 1 or more treatment-emergent adverse events	111 (83.5%)	106 (80.3%)	107 (81.7%)	213 (81.0%)

When results of treatment-emergent adverse events were classified as 'reasonably related', then the number of events recorded was higher in the q8W group (~133 events per 100 subject years) versus the q12W group (~115 events per 100 subject years), as shown in the following table extract.

TSFAE42A: Number of reasonably related treatment-emergent adverse events on induction and maintenance therapy (up to 52 weeks total) per hundred subject-years of follow-up by MedDRA system-organ class and preferred term; treated subjects randomized as responders to ustekinumab in Phase 3 Crohn's disease study (CNTO1275CRD3003)

	Placebo maintenance[a]	Ustekinumab maintenance 90 mg q12w[a]	Ustekinumab maintenance 90 mg q8w[a]	Combined
Subjects treated	133	132	131	263
Avg duration of follow-up (weeks)	40.10	44.89	43.29	44.09
Avg duration of treatment (weeks)	34.75	34.64	37.06	35.85
Total subject-years of follow-up	103	114	109	223
Number of reasonably related adverse events	179	131	145	276
Event rate per 100 subject-years	174.53	114.96	132.97	123.77
System-organ class/preferred term Infections and infestations	40.95	29.84	36.68	33.18
General disorders and administration site conditions	16.58	10.53	28.43	19.28
Skin and subcutaneous tissue disorders	12.68	11.41	18.34	14.80

The higher number of 'reasonably related' events appeared to be a function of infections, administration site conditions and skin & subcutaneous tissue disorders. The higher number of related events in the placebo group is understood to reflect symptoms of [placebo-treated] Crohn's disease.

The apparently higher rate of infection in the q8W group appeared to be reflected in the higher rate of antibiotic requirement in the q8W group (~62 events per 100 subject years) versus the q12W group (~55 per 100 subject years), as shown in the following table extract:

TSFINFE43A: Number of treatment-emergent infections requiring oral or parenteral antimicrobial treatment on induction and maintenance therapy (up to 52 weeks total) per hundred subject-years of follow-up by MedDRA system-organ class and preferred term; treated subjects randomized as responders to ustekinumab in Phase 3 Crohn's disease study (CNTO1275CRD3003)

		Ustekinumab maintenance		
	Placebo maintenance[a]	90 mg q12w[a]	90 mg q8w[a]	Combined
Subjects treated	133	132	131	263
Avg duration of follow-up (weeks)	40.10	44.89	43.29	44.09
Avg duration of treatment (weeks)	34.75	34.64	37.06	35.85
Total subject-years of follow-up	103	114	109	223
Number of infections[b] requiring treatment	53	63	68	131
Event rate per 100 subject-years	51.68	55.29	62.36	58.75

Safety in special populations

A trend in adverse event occurrence when results were analysed by sex, race, weight and severity or extent or duration of disease was not detected.

A trend in adverse event occurrence when results were analysed by extrinsic factors such as concomitant Crohn's disease medications or Crohn's disease medication history was not detected.

The company has submitted the following table of adverse event by age of recipient up to week 8 of the induction studies:

Table 28 Summary of key safety events from Week 0 to Week 8 by age group; Treated subjects in CNTO1275CRD3001 and CNTO1275CRD3002

	Age (yrs)							
	< 65		65-74		75-84		≥85	
	Placebo	Ustekinumab[a]	Placebo	Ustekinumab[a]	Placebo	Ustekinumab[a]	Placebo	Ustekinumab[a]
Analysis set: Treated subjects in CNTO1275CRD3001 and CNTO1275CRD3002	451	909	14	30	1	2	-	-
Avg duration of follow-up (weeks)	8.19	8.20	8.04	7.86	8.29	8.21	-	-
Avg exposure (number of administrations)	1.00	1.00	1.00	1.00	1.00	1.00	-	-
Total AEs	272 (60.3%)	539 (59.3%)	10 (71.4%)	19 (63.3%)	0	1 (50.0%)	-	-
Serious AEs - Total	27 (6.0%)	45 (5.0%)	1 (7.1%)	2 (6.7%)	0	1 (50.0%)	-	-
Fatal	0	0	0	0	0	0	-	-
Hospitalization/prolong existing hospitalization	27 (6.0%)	43 (4.7%)	1 (7.1%)	2 (6.7%)	0	0	-	-
Life-threatening	0	2 (0.2%)	0	1 (3.3%)	0	0	-	-
Disability/incapacity	0	0	0	0	0	0	-	-
Other (medically significant)	1 (0.2%)	6 (0.7%)	0	2 (6.7%)	0	1 (50.0%)	-	-
AE leading to study agent discontinuation	18 (4.0%)	15 (1.7%)	1 (7.1%)	1 (3.3%)	0	0	-	-
Psychiatric disorders	17 (3.8%)	15 (1.7%)	0	1 (3.3%)	0	0	-	-
Nervous system disorders	54 (12.0%)	97 (10.7%)	2 (14.3%)	2 (6.7%)	0	0	-	-
Accidents and injuries	10 (2.2%)	20 (2.2%)	0	1 (3.3%)	0	0	-	-
Cardiac disorders	3 (0.7%)	7 (0.8%)	1 (7.1%)	1 (3.3%)	0	0	-	-
Vascular disorders	5 (1.1%)	18 (2.0%)	0	0	0	0	-	-
Cerebrovascular disorders[b]	0	1 (0.1%)	0	0	0	0	-	-

Table 28 Summary of key safety events from Week 0 to Week 8 by age group; Treated subjects in CNTO1275CRD3001 and CNTO1275CRD3002

	Age (yrs)							
	< 65		65-74		75-84		≥85	
	Placebo	Ustekinumab[a]	Placebo	Ustekinumab[a]	Placebo	Ustekinumab[a]	Placebo	Ustekinumab[a]
Infections and infestations	100 (22.2%)	203 (22.3%)	3 (21.4%)	4 (13.3%)	0	0	-	-
Anticholinergic syndrome	0	0	0	0	0	0	-	-
Quality of life decreased	0	0	0	0	0	0	-	-
Sum of postural hypotension, fall, black outs, syncope, dizziness, ataxia, fractures	2 (0.4%)	5 (0.6%)	0	0	0	0	-	-

[a] Combined: Ustekinumab 130 mg IV, Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Includes adverse events: MedDRA high level group term (HLGT) of "Central nervous system vascular disorders" under MedDRA system organ class (SOC) of "Nervous system disorders".

[TEUSFAE01A.RTF] [CNTO1275\Z_ADHOC_REQ\DBR_2016_03_CD\RE_EMA_201603\PROD\TEUSFAE01A.SAS] 13APR2016, 17:39

The company has submitted the following table of adverse event by age of recipient from week 0 up to week 44 of the maintenance study:

Table 29 Summary of key safety events through Week 44 or up to the time of dose adjustment by age group; Treated subjects who were randomized in CNTO1275CRD3003

	Age (yrs)							
	< 65		65-74		75-84		≥85	
	placebo[a,c]	ustekinumab[b,c]	placebo[a,c]	ustekinumab[b,c]	placebo[a,c]	ustekinumab[b,c]	placebo[a,c]	ustekinumab[b,c]
Analysis set: Treated subjects who were randomized in CNTO1275CRD3003	129	250	3	13	1	-	-	-
Avg duration of follow-up (weeks)	31.93	35.93	30.00	36.00	43.14	-	-	-
Avg exposure (number of administrations)	6.68	7.49	6.33	7.92	10.00	-	-	-
Total AEs	108 (83.7%)	200 (80.0%)	3 (100.0%)	13 (100.0%)	0	-	-	-
Serious AEs - Total	19 (14.7%)	25 (10.0%)	1 (33.3%)	4 (30.8%)	0	-	-	-
Fatal	0	0	0	0	0	-	-	-
Hospitalization/prolong existing hospitalization	19 (14.7%)	24 (9.6%)	1 (33.3%)	4 (30.8%)	0	-	-	-
Life-threatening	1 (0.8%)	1 (0.4%)	0	0	0	-	-	-
Disability/incapacity	1 (0.8%)	0	0	0	0	-	-	-
Other (medically significant)	0	1 (0.4%)	1 (33.3%)	0	0	-	-	-
AE leading to study agent discontinuation	8 (6.2%)	14 (5.6%)	0	0	0	-	-	-
Psychiatric disorders	4 (3.1%)	13 (5.2%)	0	1 (7.7%)	0	-	-	-
Nervous system disorders	23 (17.8%)	42 (16.8%)	1 (33.3%)	1 (7.7%)	0	-	-	-
Accidents and injuries	6 (4.7%)	13 (5.2%)	0	0	0	-	-	-
Cardiac disorders	1 (0.8%)	1 (0.4%)	0	1 (7.7%)	0	-	-	-
Vascular disorders	2 (1.6%)	6 (2.4%)	0	2 (15.4%)	0	-	-	-
Cerebrovascular disorders [d]	0	0	0	0	0	-	-	-

Table 29 Summary of key safety events through Week 44 or up to the time of dose adjustment by age group; Treated subjects who were randomized in CNTO1275CRD3003

	Age (yrs)							
	< 65		65-74		75-84		≥85	
	placebo[a,c]	ustekinumab[b,c]	placebo[a,c]	ustekinumab[b,c]	placebo[a,c]	ustekinumab[b,c]	placebo[a,c]	ustekinumab[b,c]
Infections and infestations	64 (49.6%)	115 (46.0%)	1 (33.3%)	8 (61.5%)	0	-	-	-
Anticholinergic syndrome	0	0	0	0	0	-	-	-
Quality of life decreased	0	0	0	0	0	-	-	-
Sum of postural hypotension, fall, black outs, syncope, dizziness, ataxia, fractures	4 (3.1%)	5 (2.0%)	0	0	0	-	-	-

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
[b] Combined: ustekinumab 90 mg SC q12w and ustekinumab 90 mg SC q8w
[c] Includes data up to the time of dose adjustment (i.e., time of meeting loss of response criteria).
[d] Includes adverse events: MedDRA high level group term (HLGT) of "Central nervous system vascular disorders" under MedDRA system organ class (SOC) of "Nervous system disorders".

[TEUSFAE01B.RTF] [CNTO1275\Z_ADHOC_REQ\DBR_2016_03_CD\RE_EMA_201603\PROD\TEUSFAE01B.SAS] 14APR2016, 14:59

Despite small numbers of subjects in the age group of 65 to ≤ 74 years, no apparent differences in AEs, SAEs, AEs leading to study agent discontinuation, or system organ class were observed compared with subjects <65 years old. The number of subjects ≥ 75 years of age (n=3) was too small to draw any conclusions.

Table 8:	Number of subjects by age group in Crohn's disease clinical studies; Randomized subjects in C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002, and CNTO1275CRD3003			
	Age (years)			
	< 65 (n/N) [a]	65-74 (n/N) [a]	75-84 (n/N) [a]	>= 85 (n/N) [a]
Analysis set: Randomized subjects in C0379T07, C0743T26, CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003	1932	61	5	-
C0379T07 (Population 1)	100/104	4/104	0/104	-
C0743T26	507/526	16/526	3/526	-
CNTO1275CRD3001[b]	724/741	17/741	0/741	-
CNTO1275CRD3002[b,c]	601/627	24/627	2/627	-
CNTO1275CRD3003[b]	373/388	15/388	0/388	-

[a] n: number of the randomized subjects in the specified age group; N: total number of randomized subjects in the study.
[b] Excluding subjects enrolled prior to study restart.
[c] Excluding subjects from site 1127

[TEUSIDEM01.RTF] [CNTO1275\Z_ADHOC_REQ\DBR_2016_03_CD\RE_EMA_201603\PROD\TEUSIDEM01.SAS] 06APR2016, 07:54

Use in Pregnancy and Lactation

No studies of ustekinumab were conducted in pregnant or lactating women.

As of 08 July 2015, 137 reports of pregnancy were identified in studies of ustekinumab in Crohn's disease, psoriasis, PsA, MS, and healthy volunteers: 67 maternal pregnancies and 70 pregnancies with paternal exposure. Pregnancies and outcomes are presented by indication in Table 13 (maternal) and Table 14 (paternal).

Table 13:	Pregnancy outcomes with maternal exposure (cumulatively through 08 July 2015)					
Pregnancy Outcome	**Clinical Trial**					
	PSO	**PsA**	**CD**	**MS**	**Other[a]**	**Total**
Live birth	**15**	**0**	**8**	**1**	**1**	**25**
Congenital anomaly/birth defect	0	0	0	0	0	0
Other AE	2	0	0	0	0	2
No AE/congenital anomaly/birth defect	13	0	8	1	1	23
Spontaneous abortion	5	0	3	0	0	**8**
Elective abortion	9	1	4	0	1	**15**
Abortion (Unspecified)	0	0	0	0	1	**1**
Premature birth	0	0	2	0	0	**2**
Ectopic pregnancy	1	0	0	0	0	**1**
Non-viable foetus/foetal demise	0	0	1	0	0	**1**
NR/continuing	9	1	4	0	0	**14**
Total number of cases[b]	**39**	**2**	**22**	**1**	**3**	**67**

AE= adverse event; CD= Crohn's Disease; MS= Multiple Sclerosis; NR= not reported; PsA= Psoriatic Arthritis; PSO= Psoriasis.
[a]Other includes cases where indication was not reported and the case where study was a Pharmacokinetic (PK) study.
[b]Case counts include cases from long-term extension portions of the Crohn's disease study (CRD3003).

Table 14: Pregnancy outcomes with paternal exposure (cumulatively through 08 July 2015)						
Pregnancy Outcome	**Clinical Trial**					
	PSO	**PsA**	**CD**	**MS**	**Other[a]**	**Total**
Live birth	**35**	**0**	**6**	**0**	**0**	**41**
Congenital anomaly/birth defect	1	0	0	0	0	1
Other AE	4	0	0	0	0	4
No AE/congenital anomaly/birth defect	30	0	6	0	0	36
Premature birth	5	0	0	0	0	**5**
Elective abortion	1	0	2	0	0	**3**
Spontaneous abortion	3	1	2	0	0	**6**
Neonatal death	0	0	0	0	0	**0**
NR/continuing	7	2	3	1	2	**15**
Total number of cases[b]	**51**	**3**	**13**	**1**	**2**	**70**

AE= adverse event; CD= Crohn's Disease; MS= Multiple Sclerosis; NR= not reported; PsA= Psoriatic Arthritis; PSO= Psoriasis.
[a]Other includes cases where indication was not reported and the case where study was a Pharmacokinetic (PK) study.
[b]Case counts include cases from long-term extension portion of the Crohn's disease study (CRD3003).

In general, the outcomes seen in the ustekinumab pregnancies are comparable with what is expected in the general population.

Immunological events

The assays for antibodies and neutralising antibodies have been described in previous submissions.

Phase II studies

- In the C0379T07 study, none of the subjects in this study were positive for antibodies to ustekinumab.
- In the C0743T26 study, 3 subjects were positive for antibodies and none experienced an AE temporally associated with an infusion or an injection-site reaction

Phase III studies

- In the CRD3001 study, 2 subjects were positive for antibodies to ustekinumab and neither reported an AE temporally associated with an infusion during their participation in the study.
- In the CRD3002 study, 1 subject was positive for antibodies to ustekinumab through Week 20 and did not report an AE temporally associated with an infusion during participation in the study.
- In the CRD3003 study, 14 randomized subjects were positive for antibodies to ustekinumab and none experienced an injection-site reaction.

Immunogenicity of ustekinumab is described for the Phase 3 studies from Week 0 of the induction studies (CRD3001 and CRD3002) through Week 44 of the maintenance study (CRD3003), a total of 52 weeks exposure to ustekinumab [immunogenicity in the phase I and II studies was too low to permit analysis].

1,154 treated subjects received a dose of ustekinumab during induction or maintenance and had samples for antibodies. Of those, 27 subjects (2.3%; 14 in the randomized and 13 in the nonrandomized populations) were positive for antibodies to ustekinumab from Week 0 of an induction

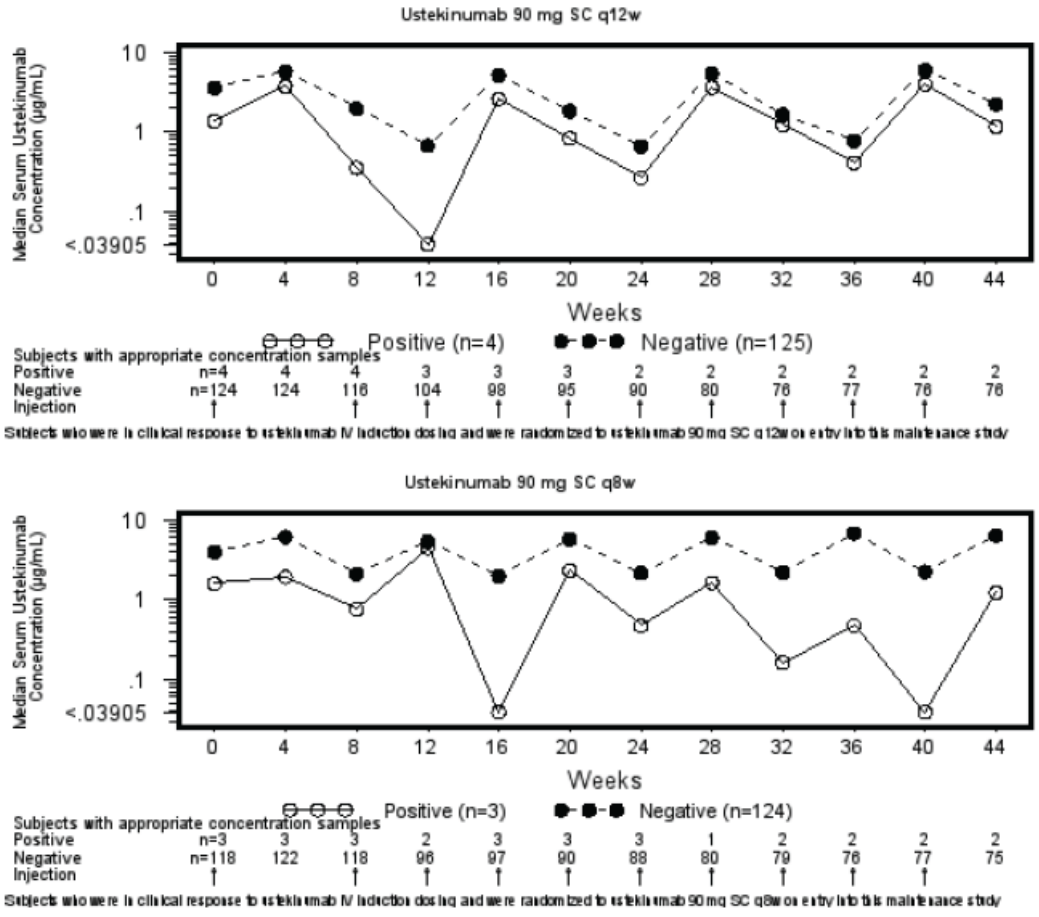
study through Week 44 of maintenance. Among these subjects who were positive for antibodies to ustekinumab, the majority (20 of 27 subjects) had titers ≤1:800.

The incidence of antibodies to ustekinumab was similar between randomized subjects who received 90 mg q12w (3.0%, 4/132 subjects) and 90 mg q8w (2.3%, 3/131 subjects).

Effect of Immunomodulators on Immunogenicity
Sample sizes are small; the proportion of subjects who were positive for antibodies to ustekinumab among those who received immunomodulators was 1.9% (7/375 subjects) compared with 2.6% (20/779 subjects) in subjects who did not receive immunomodulators.

Serum Ustekinumab Concentrations and Antibodies to Ustekinumab
The relationship between serum ustekinumab concentrations and antibody to ustekinumab status (positive or negative) in randomized subjects is shown in Figure 6.

Figure 6: **Line plot of median serum ustekinumab concentrations (micrograms/mL) over time by antibody to ustekinumab status during this maintenance study through Week 44; treated subjects who were randomized**



Median serum ustekinumab concentrations were lower in subjects who were positive for antibodies to ustekinumab compared with levels in subjects who were negative for antibodies to ustekinumab.

Neutralizing Antibodies
Of the 27 treated subjects who were positive for antibodies to ustekinumab through Week 44 of treatment with ustekinumab, 17 (63.0%) were positive for Nab.

Immunogenicity and Efficacy
Among subjects receiving maintenance ustekinumab, no apparent impact on clinical efficacy was observed following the development of antibodies to ustekinumab. Because of the limited number of subjects who were positive for antibodies to ustekinumab (<3%, the majority were neutralizing), these analyses should be interpreted with caution.

Antibodies to Ustekinumab and Safety Impact: Crohn's Disease
Overall, in the combined Crohn's disease studies, no subject who was positive for antibodies had a reaction related to study agent administration. However, due to the small number of subjects who were positive for antibodies, caution should be used in interpreting the data regarding the association of antibodies to ustekinumab and study agent administration-related events.

Relationship Between Serum Ustekinumab Concentration and Safety: Crohn's Disease
Overall, no relationship between ustekinumab exposure and safety events (ie, infections, serious infections, SAEs) were observed either for induction or maintenance at the dose levels evaluated in studies C0743T26 combined with CRD3001 and CRD3002; and the maintenance study CRD3003.

Anaphylactic and Serum Sickness like Reactions
There were no possible anaphylactic reactions or possible serum sickness-like reactions in ustekinumab-treated subjects through approximately 1 year of treatment in the Crohn's disease studies combined.

Injection-site reactions Phase 3 studies
1.7% of subjects reported a placebo injection-site reaction and 3.0% reported an ustekinumab injection-site reaction. No serious injection-site reactions or injection-site reactions of severe intensity were reported. The most frequently reported injection-site reaction among all treated subjects was the established ADR of injection-site erythema which occurred in 1.1% and 1.7% of subjects receiving a placebo or ustekinumab injection, respectively.

Safety related to drug-drug interactions and other interactions

No formal study of drug-drug interactions was performed with ustekinumab for this line extension and this was considered acceptable by the CHMP.

Discontinuation due to adverse events

Induction Phase

Pooled Data from Phase 3 Studies

The proportion of subjects who discontinued due to an AE was higher in the placebo group (4.1%) compared with the ustekinumab 130 mg IV group (1.7%) and ustekinumab ~6 mg/kg IV group (1.7%).

The SOC with the highest proportions of discontinuations was Gastrointestinal Disorders (3.2% in the placebo group, 0.8% in the ustekinumab 130 mg IV group, and 0.6% in the ustekinumab ~6 mg IV group).

These observations are not unexpected given the underlying nature of disease within the overall subject population. Other AEs leading to discontinuation generally occurred as single events without any notable patterns with regard to SOC or type of event.

Pooled Data from Phase 2 and Phase 3 Studies were consistent.

Maintenance Phase

Data from Phase 3 Study

The overall incidence of AEs leading to discontinuation was comparable between treatment groups (6.0% in the placebo group, 7.6% in the ustekinumab 90 mg SC q12w group and 3.1% in the ustekinumab 90 mg q8w group).

The SOC with the highest proportions of discontinuations was Gastrointestinal Disorders (4.5% [6 subjects] in the placebo group, 3.8% [5 subjects] in the ustekinumab 90 mg SC q12w group, and 1.5% [2 subjects] in the ustekinumab 90 mg SC q8w group)

Pooled Data from Phase 2 and Phase 3 Studies were consistent.

Post marketing experience

Post-marketing information has been accruing since the first marketing authorisation of the product in January 2009.
As of 31 December 2014, ustekinumab has been approved in 84 countries worldwide for the treatment of adult patients with chronic moderate to severe plaque psoriasis and/or active psoriatic arthritis.
The estimated cumulative worldwide exposure to ustekinumab from launch to 31 December 2014 is 379,596 person-years.

Periodic safety update reports

The cut-off date for post-marketing data in this application procedure is 31 December 2014, and through this time period, eleven Periodic Safety Update Reports have been completed.
Based on the post marketing safety surveillance, erythrodermic psoriasis, pustular psoriasis, hypersensitivity reactions (including rash, urticaria), and serious hypersensitivity reactions (including anaphylaxis and angioedema) were identified as ADRs.
The company will continue to monitor the safety profile of ustekinumab and report the safety findings as appropriate.

Postmarketing Registry: PSOLAR
Ustekinumab is also being evaluated in the Psoriasis Longitudinal Assessment and Registry (PSOLAR), a multi-centre, prospective, observational study that tracks the long-term safety experience and clinical status of patients with psoriasis who are eligible to receive (or are actively receiving) systemic therapies for psoriasis.
The post-marketing commitment for PSOLAR was to enrol 12,000 patients with moderate to severe psoriasis, including 4,000 receiving ustekinumab, with the rest receiving or eligible to receive other systemic therapies. PSOLAR enrolment has completed. As of the most recent data cut-off on 23 August 2014, 12,093 patients have enrolled in PSOLAR, with a median registry follow-up of 3.3 years, and an accumulated 40,388 patient-years of follow up.
Thus far, data analysis conducted for the PSOLAR registry has not identified any new safety signals for ustekinumab.

2.6.1. Discussion on clinical safety

The safety database from the 5 Crohn's disease clinical studies comprises 1749 ustekinumab-treated subjects (a total of 1106 subject years of follow-up) and includes 849 subjects exposed for at least 6 months, and 464 subjects exposed for at least 1 year.

Adverse events identified as related to exposure to Stelara (both intravenous and subcutaneous administrations) were consistent with known events described in the SmPC. The company has now identified the additional events: asthenia, acne, vomiting and vulvo-vaginal mycotic infection. These additional adverse events were taken over into the SmPC and are considered to be manageable with routine risk minimisation.

IV infusion was not associated with anaphylaxis or serious infusion reactions within the current development programme. Information on serious adverse events was consistent with information in the current SmPC.

Data for all subjects treated within maintenance study CRD3003 showed that infections, skin disorders (rash and itch), respiratory disorders (cough), vascular disorders (DVT), procedural complications and psychiatric disorders (depression) are more commonly associated with study drug and are reflected in the SmPC / RMP.

There were 7 subjects exposed to Stelara recorded with venous thrombosis versus 0 for placebo exposure). The company carried out a re-evaluation of cases of thrombosis after day 120 on request of the CHMP. 2 subjects were re-classified, which resulted in 8 subjects with thrombosis in the Stelara group and 1 subject with thrombosis in the placebo group.

The total number of subjects in each group (placebo and Stelara) is small in terms of the detection of harm and so it is not apparent that detailed statistical analysis is helpful. However, the event rate of DVT per 100 person years in the 'all-Stelara group' is about twice that of the placebo group i.e. 1.25 *v*. 0.63 and there may be biological plausibility for an association between ustekinumab and venous thrombotic events as interleukins are involved in the pathophysiology thrombosis and haemostasis. It is noted that further analysis by the company of other studies, post-marketing experience and a literature search did not detect an association but taken together there is a suspicion of an association and the MAH was requested to add "venous thromboembolism" as an important potential risk to the RMP. Additional pharmacovigilance for this safety concern will include monitoring as an outcome of interest in the registry study for the Crohn's disease indication as well as in the long term extension study to CRD3003 as described in the RMP.

2.3% of subjects in the clinical trials developed antibodies to Stelara. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was observed. The clinical consequences of antibody development have not yet been established in the population of Crohn's disease but this issue may be clarified when the company submits results of the on-going long-term extension of study CRD3003 as described in the RMP.

Over the course of study CRD3003, the number of treatment-emergent adverse events recorded as reasonably related' was higher in the q8W group (~133 events per 100 subject years) versus the q12W group (~115 events per 100 subject years). The higher number of 'reasonably related' events appears to be mainly a function of infections, administration site conditions and skin & subcutaneous tissue disorders and this appears to be reflected in the higher rate of antibiotic requirement in the q8W group (~62 events per 100 subject years) versus the q12W group (~55 per 100 subject years).

Since the q8W group would be administered Stelara on only 6 occasions and q12W group would be administered Stelara on only 4 occasions during the course of study CRD3003, it is considered that differences in clinical safety are likely to become more apparent on more prolonged exposure with the q8W group likely to experience more adverse events than the q12W group.

Despite small numbers of subjects in the age group of 65 to $\leqslant$74 years, no apparent differences in AEs, SAEs, AEs leading to study agent discontinuation, or system organ class were observed compared with subjects <65 years old. The number of subjects $\geq$ 75 years of age (n=3) was too small to draw any conclusions. Section 4.4 of the SmPC states that although no differences in safety profile have been seen in this population the number of elderly patients exposed is not sufficient to determine whether they respond differently from younger patients, and because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly. These statements are considered adaequate as routine risk minimisation measures.

Studies of ustekinumab were not conducted in pregnant or lactating women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. Therefore the existing precautionary statement in the SmPC to preferably avoid the use of Stelara in pregnancy is considered adequate. There is no information on exposure of Stelara to the paediatric population as the paediatric development was deferred by the PDCO.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall the safety data from the Crohn's disease studies did not appear to have altered the well characterized ustekinumab safety profile established in the approved indications of psoriasis and PsA.

Over the course of study CRD3003, the number of treatment-emergent adverse events recorded as reasonably related' was higher in the q8W group (~133 events per 100 subject years) versus the q12W group (~115 events per 100 subject years). Since the q8W group would be administered Stelara on only 6 occasions and q12W group would be administered Stelara on only 4 occasions during the course of study CRD3003, it is considered that differences in clinical safety are likely to become more apparent on more prolonged exposure with the q8W group likely to experience more adverse events than the q12W group. As this counterbalance the improved efficacy of the q8W group the initial s.c. standard dose was amended to dosing every 12 weeks (with potential increase to q8w in case if inadequate response; see also discussion on efficacy of this report).

On the basis of the limited amount of safety data available for long-term use in Crohn's disease "long-term safety in adult patients with moderately to severely active Crohn's disease" was, similar to the psoriasis and psoriatic arthritis indications included by the company into the RMP as an area of missing information. The CHMP agreed to include the ongoing long-term extension study to study CRD3003 (to evaluate the safety of 2 SC maintenance regimens) as additional pharmacovigilance activity into the RMP alongside a post-marketing registry (both category 3). The applicant committed to submit the protocol of the latter for assessment within 12 months after marketing authorisation. This study will collect information related to various outcomes, including prospective assessment of safety concerns such as malignancies and infections, analysis of the potential impact for disease modification of treatment with biologics, evaluation of the benefit-risk ratio, and appraisal of the evolution of patient-reported outcomes. Also the important potential risk "venous thromboembolism" will be monitored as an outcome of interest in the registry study.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes. The CHMP endorsed the Risk Management Plan version 13.2 with the following content:

Safety concerns

Important identified risks	• Serious systemic hypersensitivity reactions • Facial palsy • Pustular psoriasis • Erythrodermic psoriasis

Important potential risks	• Serious infections including mycobacterial and salmonella infections • Malignancy • Cardiovascular events • Serious depression including suicidality • RPLS • Venous thromboembolism • Exposure during pregnancy
Missing information	• • Use in paediatric patients (except in patients with psoriasis ≥12 years of age) • Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with a history of latent TB or TB • Use in patients with concurrent malignancy or a history of malignancy • Use after recent vaccination with live bacterial or live viral vaccines • Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C) • Use in patients with recent or concomitant use of immunosuppressive therapy other than MTX, 6-MP, AZA, 5-ASA, and corticosteroids • Use in patients with other forms of psoriasis • Use in patients who have undergone allergy immunotherapy • Long-term safety in paediatric psoriasis patients 12 years and older • Long-term impact on growth and development in paediatric psoriasis patients 12 years and older • Long-term safety in adult patients with moderately to severely active Crohn's disease

Pharmacovigilance plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
C0168Z03 (PSOLAR) (Category 3)	Primary objective: to evaluate the safety of Stelara in patients with moderate to severe plaque psoriasis (overlapping forms of psoriasis may be included)	• Serious systemic hypersensitivity reactions • Facial palsy • Pustular psoriasis • Erythrodermic psoriasis • Serious infections including mycobacterial and salmonella infections • Malignancy • Cardiovascular events • Serious depression including suicidality • RPLS • Use in patients with • hepatic impairment	Ongoing	Final Report 31 Aug 2021

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
		• Use in patients with a history of latent TB or TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C) • Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy • Use in patients with other forms of psoriasis		
CNTO1275PSO4005 (Nordic Database Initiative) (Category 3)	Primary objective: collection and analysis AEs/SAEs of interest in psoriasis patients (any form of psoriasis [ICD 10 L40]) exposed to ustekinumab, relative to the background risk in non-biologic-exposed controls	• Serious systemic hypersensitivity reactions • Facial palsy • Serious infections including mycobacterial and salmonella infections • Malignancy • Cardiovascular events • Serious depression including suicidality • RPLS • Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with a history of latent TB or TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C) • Use in patients with other forms of psoriasis	Ongoing	01 May 2020

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
CNTO1275PSO4007 (Pregnancy Research Initiative) (Category 3)	Primary objectives: to collect and analyse information pertaining to pregnancy outcomes of women exposed to ustekinumab during pregnancy and health status in the first year of life of infants born to women following prenatal exposure to ustekinumab as compared with controls.	• Exposure during Pregnancy	Ongoing	01 May 2021
Randomised, double-blind, placebo-controlled, multicentre trial (Category 3)	To evaluate the efficacy, safety, pharmacokinetics and immunogenicity of ustekinumab in children aged from 6 to less than 12 years with moderate to severe plaque psoriasis.	• Use in paediatric patients younger than 12 years	Planned	TBD
Postmarketing registry/prospective cohort observational study (Category 3)	To confirm the long-term safety profile of ustekinumab use in paediatric patients 12 years and older and to explore any potential effect on growth and development in paediatric patients 12 years and older in-line with the consideration in the STELARA PIP.	• Long-term safety in paediatric patients 12 years and older • Long-term impact on growth and development in paediatric patients12 years and older	Planned	TBD

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
CNTO1275CRD3003 Long-term extension (Category 3)	To evaluate the long-term safety of ustekinumab in adult patients with moderately to severely active Crohn's disease from Week 44 up to Week 272	• Long-term safety in adult patients with moderately to severely active Crohn's disease • Venous thromboembolism.	Ongoing	2020
Postmarketing prospective cohort observational study (Category 3)	To monitor the long-term safety profile of ustekinumab use in adult patients with moderately to severely active Crohn's disease	• Long-term safety in adult patients with moderately to severely active Crohn's disease • Evaluate incidence, relationship, and risk factors for venous thromboembolism	Planned	TBD

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks:		
Serious systemic hypersensitivity reactions	Serious systemic hypersensitivity reactions are specifically addressed in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.	In addition to the SmPC, the sponsor has implemented an educational programme that will provide further educational tools on key benefits and important potential and identified risks of ustekinumab.
Facial Palsy	Facial palsy is specifically addressed in the Undesirable Effects (4.8) section of the SmPC.	No additional risk minimisation activities are proposed.
Pustular psoriasis	Pustular psoriasis is specifically addressed in the Undesirable Effects (4.8) section of the SmPC.	No additional risk minimisation activities are proposed.
Erythrodermic psoriasis	Serious skin conditions including erythrodermic psoriasis and exfoliative dermatitis are addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC. Exfoliative dermatitis and skin exfoliation are Undesirable Effects (4.8) section of the SmPC.	The sponsor issued a DHPC to address the risk of serious skin conditions. No measure of effectiveness is planned.
Important potential risks:		
Serious infections including mycobacterial and salmonella infections	Serious infections including mycobacterial and salmonella infections are specifically addressed in the Contraindications (4.3), Special Warnings and Precautions for Use (4.4), and Undesirable Effects (4.8) sections of the SmPC.	In addition to the SmPC, the sponsor has implemented an educational programme that will provide further educational tools on key benefits and important potential and identified risks of ustekinumab.
Malignancy	Malignancy is specifically addressed in the Special Warnings and Precautions for Use (4.4) and Undesirable Effects (4.8) sections of the SmPC. The Undesirable Effects section indicates that malignancies have been reported as serious adverse reactions.	In addition to the SmPC, the sponsor has implemented an educational programme that will provide further educational tools on key benefits and important potential and identified risks of ustekinumab.
Cardiovascular events	None	No additional risk minimisation activities are proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Serious depression including suicidality	Depression is listed in the Undesirable Effects (4.8) section of the SmPC (Serious depression including suicidality is not specifically mentioned in the SmPC).	No additional risk minimisation activities are proposed.
RPLS	None	No additional risk minimisation activities are proposed.
Venous thromboembolism	None	No additional risk minimisation activities are proposed
Exposure during pregnancy	Exposure during pregnancy is addressed in the Fertility, Pregnancy, and Lactation (4.6) section of the SmPC.	No additional risk minimisation activities are proposed.
Missing information:		
Use in paediatric patients (except in patients with psoriasis ≥12 years of age)	The Posology and Method of Administration (4.2) section in the SmPC indicates that safety in patients with psoriasis less than 12 years of age and in patients with psoriatic arthritis and Crohn's disease less than 18 years of age has not yet been established.	No additional risk minimisation activities are proposed.
Use in renal impairment	This safety concern is addressed in the Posology and Method of Administration (4.2) and the Pharmacokinetic Properties (5.0) sections of the SmPC.	No additional risk minimisation activities are proposed.
Use in hepatic impairment	This safety concern is addressed in the Posology and Method of Administration (4.2) and the Pharmacokinetic Properties (5.0) sections of the SmPC.	No additional risk minimisation activities are proposed.
Use in patients with a history latent TB or TB	This safety concern is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	No additional risk minimisation activities are proposed.
Use in patients with concurrent malignancy or a history of malignancy	This safety concern is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	No additional risk minimisation activities are proposed.
Use after recent vaccination with live bacterial or live viral vaccines	Use after recent vaccination with live bacterial or live viral vaccines is addressed in the Special Warnings and Precautions for Use (4.4) and the Interaction with Other Medicinal Products and Other Forms of Interaction (4.5) sections of the SmPC.	No additional risk minimisation activities are proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Use in patients with active infections (eg, TB, HIV, hepatitis B, or hepatitis C)	This safety concern is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	No additional risk minimisation activities are proposed.
Use in patients with recent or concomitant use of immunosuppressive therapy other than MTX, 6-MP, AZA, 5-ASA, and corticosteroids	Use in patients with recent prior use of other biologic therapy or receiving concomitant immunosuppressive therapy is addressed in the Special Warnings and Precautions for Use (4.4) and Interaction with Other Medicinal Products and Other Forms of Interaction (4.5) sections of the SmPC.	No additional risk minimisation activities are proposed.
Use in patients with other forms of psoriasis	None	No additional risk minimisation activities are proposed.
Use in patients who have undergone allergy immunotherapy	Use in patients who have undergone allergy immunotherapy is addressed in the Special Warnings and Precautions for Use (4.4) section of the SmPC.	No additional risk minimisation activities are proposed.
Long-term safety in paediatric psoriasis patients12 years and older	Section 4.2 of the SmPC highlights that the physician should ensure appropriate follow-up of patients. STELARA has not been studied beyond 60 weeks in children 12 years and older. However, long-term safety follow-up data will be collected in this patient population.	No additional risk minimisation activities are proposed.
Long-term impact on growth and development in paediatric psoriasis patients 12 years and older	Section 4.2 of the SmPC highlights that the physician should ensure appropriate follow-up of patients. STELARA has not been studied beyond 60 weeks in children 12 years and older. However, long-term safety follow-up data will be collected in this patient population.	No additional risk minimisation activities are proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Long-term safety in adult patients with moderately to severely active Crohn's disease	Section 4.2 of the SmPC highlights that the physician should ensure appropriate follow-up of patients. STELARA has not been studied beyond 52 weeks of continuous treatment. However, long-term safety follow-up data will be collected in this patient population.	No additional risk minimisation activities are proposed.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- The design and layout of the proposed Stelara IV and SC PLs will match the existing Stelara SC PL design and layout and is in accordance with the applicable EU guidelines. No changes that may affect its readability are expected.
- The PLs for the Stelara IV and SC presentations included in the application are based upon the currently approved Stelara SC PL. User testing in compliance with the above mentioned legislative requirements was performed on the Stelara SC PL at the time of the initial marketing authorization application procedure, which was approved on 16 January 2009.
- Additional user consultation testing was performed in July 2015, as part of the procedure to extend the psoriasis indication to include children from 12 to 18 years of age (procedure EMEA/H/C/00958/II/0042). In general, readability of the currently approved Stelara SC PL in the adult and adolescent patient groups fulfilled the EU requirements for user testing, however some changes to the layout of multi-lingual leaflets are required. This change will also be implemented for the new 130 mg concentrate for solution for infusion presentation.
- The Applicant believes that the contents of the proposed Stelara IV and SC PLs have not significantly changed compared to the currently approved Stelara SC PL. For both the SC and IV PLs, the changes are related to the addition of the new indication Crohn's disease and have an impact on section 1 "What Stelara is and what it is used for", section 3 "How to use Stelara" and to a limited extent on section 4 "Possible side effects".
- IV induction: the Instructions For Use (IFU) at the end of the Stelara IV PL have changed,

however, as Stelara (ustekinumab) 5.0 mg/mL concentrate for solution for infusion, is a prescription medicine intended for IV administration to patients by healthcare professionals in a hospital setting, there is no impact for patients.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Crohn's disease is a chronic inflammatory disorder that can affect any part of the gastrointestinal tract. Patients present with persistent diarrhoea, abdominal pain and weight loss.
The indication claimed is:
STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, were intolerant to, or have medical contraindications to either:

- Conventional therapy, or
- TNFα antagonist therapy.

The beneficial effects that are important in the management of Crohn's disease are induction and maintenance of remission (i.e. resolution of all signs and symptoms of Crohn's disease) in association with endoscopic and histological evidence of maintenance of lack of pathology in the gut mucosa. Reduction (and preferably stopping) in exposure to corticosteroids is also considered to be important.

3.1.2. Available therapies and unmet medical need

The current standard of medical care for Crohn's disease involves anti-inflammatory therapeutic approaches, which include 5-aminosalicylic acid (5-ASA) compounds, corticosteroids, immune-modulators including azathioprine (AZA) or its active metabolite 6-mercaptopurine (6-MP) and methotrexate (MTX), and biologic agents including tumour necrosis factor (TNF) antagonist therapies and anti-integrin therapies. Even with combinations of the available therapeutic options, many patients do not attain clinical benefit or cannot tolerate the therapy.
All agents have significant adverse event profiles. Among patients who receive TNF antagonist therapies for Crohn's disease, 20% to 40% are primary non-responders and among those with an initial response, ~40% lose their response over time.

3.1.3. Main clinical studies

The clinical picture of Crohn's disease may be described using the CDAI tool; the company has used the CDAI tool to establish the baseline status of subjects enrolled into the clinical studies and to follow progress. The company has undertaken an endoscopy sub-study with histology of biopsies and exposure to corticosteroids was assessed consequent to exposure to Stelara in the main clinical studies.

Studies CRD3001 and CRD3002 were randomized, double-blind, placebo-controlled, parallel-group, multi-centre studies. The target population in both studies consisted of men or women ≥18 years old with moderately to severely active Crohn's disease (of at least 3 months duration), defined as a CDAI score of ≥220 and ≤450.

In ***CRD3001***, subjects had received infliximab, adalimumab or certolizumab pegol at a dose approved for the treatment of Crohn's disease, and either did not respond initially, responded initially but then lost response or were intolerant to the medication.

CRD3002 included subjects who had failed conventional therapy (ie immunomodulators and / or corticosteroids; including subjects who were corticosteroid-dependent). Subjects in CRD3002 could have been treated with TNF antagonist therapy in the past but must not have met the failure criteria specified for CRD3001. Subjects were permitted to receive concomitant Crohn's disease medications; the dosage was to remain stable (including corticosteroids) without initiation or increase through Week 8.

All subjects were randomized in a 1:1:1 ratio to receive a single IV administration of placebo or 1 of 2 induction doses of ustekinumab at Week 0:

- Placebo
- Ustekinumab 130 mg
- Ustekinumab ~6 mg/kg

At Week 6, all subjects were evaluated for the primary endpoint of clinical response (defined as a reduction in CDAI of ≥100 points or to <150 for subjects with a baseline score ≥220 to ≤248).

Those subjects who achieved clinical response under ustekinumab at week 8 were eligible to enter study CRD3003 as the primary population.

Study CRD3003 was a multi-centre, placebo-controlled, parallel-group, double-blind, randomized withdrawal study to evaluate the safety and efficacy of SC regimens of ustekinumab maintenance therapy in subjects with moderately to severely active Crohn's disease who were induced into clinical response with IV ustekinumab. The maintenance portion of the study was through Week 44 [a subsequent study extension will continue up to Week 272].

The primary population was those who were in clinical response to IV ustekinumab induction therapy at Week 8 of either the CRD3001 or CRD3002 induction studies.

Subjects in the primary population were randomized at Week 0 of the maintenance study to 1 of the following 3 treatment groups:

- Placebo
- Ustekinumab 90 mg SC every 12 weeks (q12w; with final dose at Week 36)
- Ustekinumab 90 mg SC every 8 weeks (q8w; with final dose at Week 40)

Subjects underwent tapering off of oral corticosteroid medications. All other Crohn's disease-related medications were to remain stable through Week 44 of the maintenance study.

The primary end-point was clinical remission at Week 44 where clinical remission is defined as a CDAI score of < 150 points.

3.2. Favourable effects

Study CRD3001

- The proportion of subjects in clinical response at Week 6 (the primary endpoint) was greater in both the ~6 mg/kg (33.7%) and 130 mg (34.3%) ustekinumab groups than in the placebo group (21.5%; p=0.003 and p=0.002, respectively).

- The proportion of subjects in clinical remission at Week 8 (the first major secondary endpoint) was greater in both the ~6 mg/kg (20.9%) and 130 mg (15.9%) ustekinumab groups than in the placebo group (7.3%; p<0.001 and p=0.003, respectively).

Study CRD3002

- The proportions of subjects in clinical response at Week 6 (primary endpoint) were greater in both the ~6 mg/kg (55.5%) and 130 mg (51.7%) ustekinumab groups than in the placebo group (28.7%, p<0.001 for both comparisons).

- The proportions of subjects in clinical remission at Week 8 (the first major secondary endpoint) were greater in both the ~6 mg/kg (40.2%) and 130 mg (30.6%) ustekinumab groups than in the placebo group (19.6%, p<0.001 and p=0.009, respectively).

Both studies CRD3001 and CRD3002 met their primary end-points.

Study CRD3003

For the primary endpoint of clinical remission at Week 44, a higher proportion of subjects in the 90mg ustekinumab QW8 and 90mg ustekinumab QW12 groups were in clinical remission at Week 44 (53.1% and 48.8%, respectively) compared with the placebo group (35.9%; p=0.005 and p=0.040, respectively). The study met its primary end-point.

The major secondary endpoint of corticosteroid-free remission at Week 44 in CRD3003 was achieved by a greater proportion of subjects in the ustekinumab 90 mg q12w and q8w groups (42.6% and 46.9%, respectively) compared with the placebo group (29.8%).

In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline in the number of fistulae draining upon gentle compression) compared to 5/11 (45.5%) exposed to placebo.

For those exposed to Stelara, both serum CRP concentration and fecal content of calprotectin fell over the first 8 weeks of induction compared to placebo, presumably reflecting a reduction in inflammatory burden for those who received Stelara. Thereafter in the maintenance phase, both serum CRP concentration and fecal content of calprotectin were relatively stable over the course of 44 weeks in those who received Stelara.

For those exposed to Stelara, both the IBDQ and SF-36 scores rose over the first 8 weeks of induction compared to results for the placebo group. Scores were relatively constant thereafter in the Stelara group over the course of the 44 week maintenance phase. Further, the results of the work limitations questionnaire, time lost from work questionnaire and the productivity visual analogue scale did not convince of difference between the Stelara and placebo groups over the course of the maintenance phase.

Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a sub-study. At week 8, after a single intravenous induction dose, the primary endpoint of change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease

(SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. The change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p=0.012).

95 subjects went forward for endoscopy in study CRD3003. A statistically significant difference in SES-CD score between study drug and placebo groups was not found at week 44. The high fall-out of subjects over the maintenance study and consequent potential for selection bias makes it difficult to interpret results from the maintenance phase.

Durable clinical remission was defined by the company as a post hoc exercise that required subjects in clinical response at baseline in study CRD3003 to be in remission at 80% of visits prior to Week 44 and also at Week 44 (i.e. at least 9 of 11 visits in the CRD3003 study). 37% of subjects in the combined Stelara group were in durable clinical remission versus 23.7% of subjects in the placebo group (p<0.005). Results are consistent with the primary endpoint of study CRD3003.

3.3. Uncertainties and limitations about favourable effects

When considering remission over time in the subset of responding subjects that were in remission upon entry to CRD3003 (i.e. remission in remitters), there was a gradual decline over time to 66.7% at Week 44 in the q8w group (with a lower proportion of 56.4% on q12w) i.e. (about) 40% reduction in clinical remission over the course of study CRD3003.

Similarly, for clinical response, there was a gradual 40% reduction in the proportion of subjects who remained in clinical response.

It is considered that it has not established whether 'loss of remission' or 'loss of response' reach a plateau within 44 weeks or whether loss of remission and response is on-going. Data are provided in 5.1 of the SmPC so that prescribers are informed about the efficacy maintenance profile of Stelara which is considered satisfactory. It is anticipated that this issue may be clarified by the proposed extension study to study CRD3003.

3.4. Unfavourable effects

Major issues were not identified by the clinical assessment.

Adverse events identified as related to exposure to Stelara (both intravenous and subcutaneous administrations) were consistent with known events described in the SmPC. The company has now identified, in addition: asthenia, acne, vomiting and vulvo-vaginal mycotic infection. These additional adverse events were taken over into the SmPC and are considered to be manageable with routine risk minimisation.

Over the course of study CRD3003, the number of treatment-emergent adverse events recorded as 'reasonably related' was higher in the Q8W group (~133 events per 100 subject years) versus the Q12W group (~115 events per 100 subject years). The higher number of 'reasonably related' events appears to be mainly a function of infections, administration site conditions and skin & subcutaneous tissue disorders and this appears to be reflected in the higher rate of antibiotic requirement in the Q8W group (~62 events per 100 subject years) versus the Q12W group (~55 per 100 subject years).

Subsequently the s.c. standard dose was amended to dosing every 12 weeks (with potential increase to q8w in case if inadequate response.

3.5. Uncertainties and limitations about unfavourable effects

When events of both thrombosis and deep vein thrombosis were considered together in the safety data up to week 44 in CRD3003 the event rate per 100 patient-years was 1.25 (95% CI 0.57 – 2.38) for all ustekinumab and 0.63 (0.02 – 3.53) for placebo. The point estimate for ustekinumab is higher than for placebo, although the confidence intervals are wide and overlapping.

The overall evidence did not suggest a causal relationship with ustekinumab but as a biologic plausibility for IL-12/23 inhibitors to induce venous thrombosis exists venous thromboembolism was included as an important potential risk into the RMP.

Information in elderly is very sparse. Although no differences in safety profile have been seen in this population there is a higher incidence of infections in the elderly population in general and a precautionary statement was added in 4.4. of the SmPC .

3.6. Effects Table

Table 1. Effects Table for Stelara in the indication of Crohn's disease.

(a) Induction

Effect	Short Description	Unit	IV UST ~6mg/kg	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
CDAI score	Clinical response (5) at week 6	%	33.7	21.5	p=0.003 vs placebo	(1)
		%	55.5	28.7	p<0.001 vs placebo	(2)
	Clinical remission (6) at week 8	%	20.9	7.3	p<0.001 vs placebo	(1)
		%	40.2	19.6	p<0.001 vs placebo	(2)
					Strengths: clinical studies were randomised, placebo-controlled, double-blinded	
					Weaknesses: company has used clinical response instead of clinical remission as primary end-point. Induction studies lasted only 8 weeks; a 16-week exposure would have been preferred (2 administrations)	
Unfavourable Effects						

Effect	Short Description	Unit	IV UST ~6mg/kg	Placebo	Uncertainties/ Strength of evidence	References
Adverse events	Any treatment-emergent adverse event	%	60.4	60.5	Strengths: adverse events were essentially similar to those already established for Stelara	(4)
	Any treatment emergent serious adverse event	%	5.3	6.0		(4)

(b) Maintenance

Effect	Short Description	Unit	SC UST 90mg q8w	SC UST 90mg q12w	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects							
CDAI score	Clinical remission (6) at week 44	%	53.1	48.8	35.9	q8w: p=0.005 q12w: p=0.040 vs. placebo	(3)
	Clinical remission (6) at week 44 in patients in remission at week 0	%	66.7	56.4	45.6	q8w: p=0.007 q12w: p=0.189 vs. placebo	(3)
						Strength: clinical study was randomised, placebo-controlled, double-blinded. Primary end-point was clinical remission.	
						Weaknesses: For those who were in clinical remission at baseline in the maintenance study, only 60% were still in remission by week 44. Long term effects on clinical remission await outcome of extension study.	
Unfavourable Effects							
Adverse events	Any adverse event	%	81.7	80.3	83.5	Strengths: adverse events were essentially similar to those already established for Stelara	(3)
	Any treatment emergent serious adverse event	%	9.9	12.1	15.0		(3)
	'reasonably related' adverse event	No. per 100	133	115		Higher rate of infection/admin disorders/skin	(3)

Effect	Short Description	Unit	SC UST 90mg q8w	SC UST 90mg q12w	Placebo	Uncertainties/ Strength of evidence	References
	number	subj. years				disorders in Q8W group versus Q12W group	
	Antibiotic requirement		62	55			(3)

Abbreviations: UST: Ustekinumab

Table 2. Notes: (1) Study CRD-3001 in TNF antagonist failures (2) Study CRD-3002 in conventional therapy failures (3) Study CRD-3003 in patients in response after induction therapy with ustekinumab in CRD-3001 or CRD-3002 (4) Pooled data from CRD-3001 and CRD-3002 (5) Reduction from baseline of ≥ 100 points or score <150 (6) Score < 150Benefit-risk assessment and discussion.

3.6.1. Importance of favourable and unfavourable effects

The attainment of clinical remission in subjects with Crohn's disease who have not responded to current therapies is considered to be very important.

The reduction in corticosteroid exposure is also important because of the adverse events associated with corticosteroids though not all subjects were able to stop corticosteroids; further, the reduction in adverse events of corticosteroid exposure needs to be counterbalanced by the adverse events associated with exposure to Stelara.

From a clinical perspective, unfavourable effects identified in the development programme for Stelara in the management of Crohn's disease mainly reflect unfavourable effects that are already known from the previous development programme in psoriasis namely nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis. It is considered that the unfavourable effects are tolerable and amenable to clinical management.

3.6.2. Balance of benefits and risks

Stelara is considered to meet an unmet medical need by offering clinical efficacy to those patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

The new mode of administration (induction treatment with intravenous and maintenance treatment with subcutaneous administration) can be considered a clinical benefit compared to intravenous administered therapies.

The attainment of clinical remission in subjects with Crohn's disease who have not responded to current therapies coupled with reduction in exposure to corticosteroids far outweighs the unfavourable effects, especially since the unfavourable effects are considered to be tolerable and amenable to clinical management.

3.6.3. Additional considerations on the benefit-risk balance

In study CRD3003, the increase in absolute rate of clinical remission at week 44 for q8w administration versus q12w was 4.3% (rate ratio 1.09) and the increase in absolute rate of clinical response at week 44 for q8w administration versus q12w was 1.3% (rate ratio 1.02). The q8w administration was associated with a higher frequency of 'related' adverse events compared to q12w administration; it is considered that the difference in clinical safety between the two frequencies of administration will become more apparent with more prolonged exposure. Further, the higher rate of adverse events associated with the q8w administration is considered to counterbalance the increased efficacy associated with the q8w frequency such that the overall benefit risk balance of the q8w and q12w frequencies are considered to be equivalent. Therefore, the s.c. standard dose (after the first s.c. dose applied 8 weeks after the intravenous dose) was amended to dosing every 12 weeks (with potential increase to q8w in case of inadequate response).

3.7. Conclusions

The overall B/R of Stelara is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of the line extension on Stelara, 5 mg/ml concentrate for solution for infusion, 45 mg and 90 mg solution for injection and prefilled syringe is favourable in the following indication:

STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

The CHMP therefore recommends the granting of the marketing authorisation.

Other conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

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

- Healthcare professional educational pack
- Patient information pack

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

- Summary of product characteristics
- Local guidance for tuberculosis screening;
- Risk of serious infections, including salmonella, tuberculosis, and other mycobacterial infections;
- Risk of hypersensitivity reactions, including allergy to latex present in the needle cover of the pre-filled syringe;
- Risk of malignancies.

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

- Package leaflet
- Risk of reactivation of latent tuberculosis and information about the screening for tuberculosis according to the local guidance;
- Risk of serious infections, including salmonella, tuberculosis, and other mycobacterial infections;
- Risk of hypersensitivity reactions, including allergy to latex present in the needle cover of the pre-filled syringe;
- Potential risk of malignancies;
- Appropriate techniques for self administration of Stelara, including use of the prefilled syringes.

Additional Data/Marketing protection

Furthermore, the CHMP reviewed the data submitted by the Janssen-Cilag International N.V., taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and Commission "*Guidance on elements required to support the significant benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11 years) marketing protection period*, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies"