CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761044Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA	**761044 (eCTD sequence 0000)**
Drug Name	**Ustekinumab (Stelara)**
Formulation	**Sterile (b) (4) solution for intravenous (IV) infusion and (b) (4) solution for subcutaneous (SC) injection**
Formulation Strength	**130 mg/26 mL (5 mg/mL) for IV infusion and 90 mg/mL for SC injection**
Dosing Regimen	**Weight-based tiers dosing of approximately 6 mg/kg IV for induction x 1, and then 90 mg SC Q8W**
Route of Administration	**IV followed by SC administration**
Description of Submission	**Original BLA**
Received Date	**11/25/15**
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Applicant	**Janssen Biotech, Inc.**
Proposed Indication	**Treatment of moderate to severe Crohn's disease in patients who have failed/were tolerant to immunomodulators or (b) (4)**

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APPEARS THIS WAY ON ORIGINAL

1. EXECUTIVE SUMMARY

The Applicant submitted an original Biologics License Application (BLA) 761044 for ustekinumab (STELARA®, CNTO1275) for the treatment of moderately to severely active Crohn's disease (CD). Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody (mAb) to the p40 subunit common to human interleukin-12 (IL-12) and IL-23. It binds with high affinity to human IL-12 and IL-23 and neutralizes their bioactivity by preventing these cytokines from binding to their shared cell-surface receptor chain, IL-12Rβ1 (IL-12 receptor beta-1), expressed on the surface of immune cells.

Ustekinumab has previously been approved for the treatment of chronic moderate to severe plaque psoriasis and acute psoriatic arthritis (PsA) in adults (BLA 125261).

Proposed indication: For the treatment of adult patients (b) (4) with moderately to severely active Crohn's disease (CD) who have:

- Failed or were intolerant to immunomodulators or corticosteroids, but never failed (b) (4) (b) (4) or
- Failed or were intolerant to (b) (4)

Proposed dosing regimens for the CD indication:

(b) (4)

Proposed dosage forms/presentations:
Solution for IV infusion: 130 mg/26 mL in a (b) (4) vial
For subcutaneous (SC) injection: 45 mg/0.5 mL in a (b) (4) prefilled syringe and 90 mg/mL in a (b) (4) prefilled syringe,

The current submission contains data from six clinical trials. It includes one phase 1 study in healthy subjects (NAP1002), and two phase 2 studies (C0379T07 and C0743T26) and three phase 3 studies (CRD3001, CRD3002 and CRD3003) in subjects with moderately to severely active CD.

1.1 Recommendation

From a clinical pharmacology perspective, information submitted in this BLA is acceptable to support the BLA approval, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

For the induction dosing, the proposal of a single IV dose of ustekinumab of approximately 6 mg/kg using weight-based tiers as specified above is acceptable.

For the maintenance dosing, the proposed dosing regimen of ustekinumab 90 mg SC q8w is acceptable. (b) (4)

[redacted]

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1.2 Phase 4 Requirements/Commitments

The Clinical Pharmacology review team recommends the following post-marketing commitment (PMC):

Conduct a clinical trial to assess whether ustekinumab alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in CD patients treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs). This recommendation is based on the current understanding that CD patients have elevated levels of proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon the disease improvement following the ustekinumab treatment.

1.3 Summary of Clinical Pharmacology Findings

Pharmacokinetics (PK) of Ustekinumab IV in Subjects with Moderate and Severe CD

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

A two-compartment structural model with first-order absorption for SC administration adequately described population PK (PopPK) of ustekinumab. The typical value of ustekinumab clearance (CL) in a subject weighing approximately 70 kg was 0.191 L/day (95% confidence interval [CI]: 0.185 to 0.197 L/day), and the central volume of distribution (V2) was 2.74 L (95% CI: 2.69 to 2.78 L). The between subject variability was 29.1% for CL and 14.7% for V2. The estimated bioavailability of ustekinumab following SC administration was 78.3% while the median terminal elimination half-life of was ~19 days. After chronic dosing of ustekinumab in the maintenance phase, ustekinumab PK did not appear to change.

Although the PopPK modeling analysis identified multiple significant covariates affecting the CL and V2 parameters, the impact of these covariates was within ± 20% and considered not clinically meaningful.

After the first maintenance dose at Week 0, the steady-state appeared to have been reached at Week 12 or Week 8 prior to the administration of the second maintenance dose for ustekinumab 90 mg SC q12w and 90 mg SC q8w, respectively. The median serum ustekinumab trough

concentrations in the ustekinumab 90 mg SC q8w group appeared consistent from Week 8 through Week 44 ranging from 1.97 to 2.24 µg/mL. The median serum ustekinumab trough concentrations in the ustekinumab 90 mg SC q12w group also appeared consistent from Week 12 through Week 44, with a range of 0.61 to 0.76 µg/mL.

Dose-Response (D-R)/Exposure-Response (E-R) Relationships

Efficacy:

There were dose-dependent and concentration-dependent increases in clinical efficacy of ustekinumab for both the induction dose and the maintenance dosing regimen.

For the induction dose, higher proportions of subjects achieved clinical remission at Week 8 in the ~6 mg/kg IV dose group than the 130 mg IV dose group in subjects who have (20.9% vs. 15.9%) or have not (40.2% vs. 30.6%) failed tumor necrosis factor α (TNFα) antagonist. The clinical remission rates of the ~6 mg/kg and the 130 mg dose group were significantly higher than the clinical remission rate in the placebo group for both patient populations (7.3% in the TNFα antagonist failure population [$p = 0.003$ and $p < 0.001$, respectively] and 19.6% in the TNFα antagonist non-failure population [$p < 0.001$ and $p = 0.09$, respectively]) .

For the maintenance dosing regimen, the proportion of subjects who achieved clinical remission at Week 44 was higher in the 90 mg/kg SC q8w group than the 90 mg SC q12w group for subjects who have (41.1% vs. 38.6%) or have not (62.5% vs. 56.9%) failed previous TNFα antagonist. The clinical remission rate at Week 44 in the 90 mg SC q8w group was significantly higher than the clinical remission rate in the placebo group for the TNFα antagonist non-failure population (44.3%, $p = 0.02$) but not for the TNFα antagonist failure population (26.2%, $p = 0.102$). Nonetheless, the study was designed to detect the differences in clinical remission rate among the different dose groups for the entire study population (i.e., TNFα antagonist failure plus non-failure subjects); it would have been underpowered to detect the differences in clinical remission rate among different dose groups in either the TNFα failure or non-failure population.

Results from E-R analysis showed that clinical remission rate at Week 8 during induction was near plateau at ustekinuamb concentrations of 5 – 10 µg/mL in subjects who have or have not failed TNFα antagonist (Figure 5, left panel), whereas for maintenance phase a plateau was reached at ustekinumab concentrations of 2 – 5 µg/mL in subjects who have not failed TNFα antagonist (Figure 5, right panel). There was no E-R relationship for maintenance therapy in subjects who have failed TNFα antagonist.

Among subjects who were randomized to ustekinumab 90 mg SC q12w, met loss of response (LOR) criteria and had a dose adjustment to 90 mg SC q8w, approximately 40% achieved clinical remission 16 weeks later, compared with 32% remission rate in subjects in the ustekinumab 90mg SC q8w who met LOR criteria and remained on the 90 mg SC q8w regimen. The ~8% improvement in clinical remission by increasing dosing frequency from q12w to q8w in subjects who lost response over subjects without dose adjustment suggested that the 90 mg SC q8w was more effective in achieving clinical remission than the 90 mg SC q12w.

Safety:

Overall, the incidence of adverse events (AEs), serious adverse events (SAEs), infections, and serious infections appeared similar between the 130 mg and ~6 mg/kg dose groups in the induction phase. The incidence of these safety events appeared similar across the serum ustekinumab concentration quartiles during induction.

There appears to be a slightly higher incidence of serious infections in the ustekinumab 90 mg SC q12w group than the ustekinumab 90 mg SC q8w during the maintenance phase up to the point of dose adjustment. While the number of serious infections was small and the duration of follow up was short, this finding should be taken into consideration when comparing the two dosing regimens.

Recommended Dosing Regimen

The D-R relationship supports the following recommended dosing regimens:

- A single induction dose of ustekinumab ~6 mg/kg IV followed by a maintenance regimen of ustekinumab 90 mg SC q8w.

The E-R relationship provides supportive evidence of clinical efficacy for the above recommended dosing regimens.

Drug-Drug Interactions

No formal drug-drug interaction studies or disease-drug-drug interaction studies were conducted for ustekinumab in CD. The concomitant use of immunomodulators including 6-mercaptopurine (6-MP), azathioprine (AZA) and methotrexate (MTX) did not appear to affect ustekinumab concentrations based on the comparison of median observed ustekinumab concentration over 44 weeks and PopPK analysis.

Immunogenicity

Twenty-seven of 1154 (2.3%) treated subjects who received at least one dose of ustekinumab during induction or maintenance were positive for antidrug antibodies (ADA) in the phase 3 trials. Seventeen of the 27 (63%) subjects were positive for neutralizing antibodies (NAb).

The concomitant use 6-MP, AZA, and MTX had an impact on immunogenicity. The proportion of ADA+ subjects was lower among those who received immunomodulators (7/375 subjects, 1.9%) compared with those who did not receive immunomodulators (20/779 subjects, 2.6%)

Impact of immunogenicity on PK, Efficacy, and Safety

Immunogenicity had a negative impact on PK. While the PopPK model predicted a 13% higher CL in ADA+ subjects, the median observed serum ustekinumab concentrations were approximately two to three-fold lower in subjects who were ADA+ than in subjects who were ADA-. At the individual subject level, the mean ustekinumab concentration in ADA+ samples

was reduced by 42.8% to 89.1% when compared to the mean ustekinumab concentration in ADA- samples.

The assessment of the impact of immunogenicity on clinical efficacy is inconclusive because the number of subjects who became ADA+ was small in the phase 3 studies.

The development of antibodies to ustekinumab did not appear to be associated with injection-site reactions. However, the results should be interpreted with caution because of the infrequent assessment of immunogenicity in the CD clinical trials.

PK Comparability of 90 mg/mL Liquid-in-Vial (LIV) formulation (Currently Marketed) and 5 mg/mL LIV formulation (To-be-Marketed)

The PK comparability was established between the proposed to-be-marketed 5 mg/mL LIV formulation and the currently marketed 90 mg/mL LIV formulation when administered intravenously (IV) at 6 mg/kg dose.

The geometric mean ratio of maximal concentration (C_{max}) between the two formulations was 0.967, with a 90% CI of 0.932 to 1.003. The geometric mean ratios (90% CI) for the area under the concentration-time curve from zero to infinity (AUC_{inf}) and the area under the concentration-time curve from zero to the last quantifiable concentration (AUC_{last}) were the 0.971 (0.914 – 1.031) and 0.971 (0.920 – 1.024), respectively.

2. QUESTION BASED REVIEW

2.1 List the Clinical Pharmacology and the clinical studies with PK and/or PD information submitted in the BLA

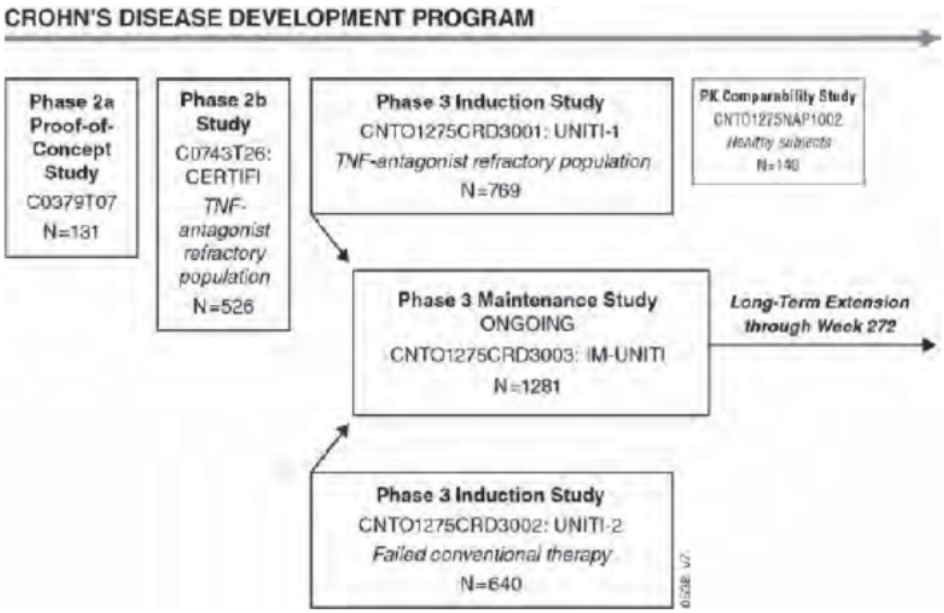
The ustekinumab clinical development program for the treatment of moderately to severely active CD included one phase 1 (NAP1002) study in healthy subjects, and two phase 2 studies (C0379T07 and C0743T26) and three phase 3 studies (CRD3001, CRD3002 and CRD3003) in subjects with moderate to severe active CD (Figure 1). Data from these studies are used to support the clinical pharmacology section of this BLA submission (Table 1).

Table 1: Clinical trials and clinical pharmacology studies that support the BLA.

Clinical Trials	Brief description of study design (number of subjects enrolled)	Dosing regimen	Clinical Pharmacology data
Phase 1			
CNTO1275NAP1002	Phase 1, Randomized, Open-label, Parallel-design Study to compare single-dose PK of intravenous Ustekinumab delivered in two different liquid in vial Formulations (n=140 healthy subjects)	6 mg/kg IV infusion x1 Reference: 90 mg/mL LIV Test: 5 mg/mL LIV	– PK comparability data – PK: NCA; samples analyzed using ECLIA assay – Immunogenicity: samples analyzed using ECLIA assay
Phase 2			
C0379T07	Phase 2a, multi-center, randomized, placebo-controlled, multiple-dose study (131 patients). Population 1 (n=104): Patients with Crohn's disease despite treatment with 5-ASA compounds, antibiotics, corticosteroids, and/or immunomodulators, including TNF antagonists. Population 2 (n=27): Patients who failed to respond to, or lost response to, infliximab at the maximum approved dose and treatment regimen for Crohn's disease.	4.5 mg/kg IV infusion x 1 or 90 mg SC qw x 4	– PK: NCA; samples analyzed using ELISA assay. Data from the study not included in the final PopPK analysis – PD – Immunogenicity: samples analyzed using EIA assay (not drug tolerant) – Efficacy/safety
C0743T26	Phase 2b multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study in patients with moderately to severely active Crohn's disease previously treated with TNF antagonist therapy (n = 526)	Placebo, 1, 3, or 6 mg/kg IV x 1 at Week 0, followed by 90 mg SC at Week 8 and Week 16	– PK: descriptive, PopPK; sample analyzed using ECLIA method – Dose ranging – PD – Immunogenicity: samples analyzed using EIA assay (not drug tolerant) – Efficacy/safety

Phase 3			
CNTO1275CRD 3001	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in patients with moderately to severely active Crohn's disease who have failed or are intolerant to TNF antagonist therapy(n=741)	Induction: Placebo, 130 mg, or ~6 mg/kg (tiered dosing by weight) IV x 1 at Week 0	− PK: descriptive, PopPK; sample analyzed using ECLIA method − PD − Immunogenicity: samples analyzed using ECLIA assay − Efficacy/safety
CNTO1275CRD 3002	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in patients with moderately to severely active Crohn's disease (n=640) CRD3002 included subjects with evidence of active inflammation who had failed conventional therapy (i.e., immunomodulators and/or corticosteroids).	Induction: Placebo, 130 mg, or ~6 mg/kg (tiered dosing by weight) IV x 1 at Week 0	− PK: descriptive, PopPK; sample analyzed using ECLIA method − PD − Immunogenicity: samples analyzed using ECLIA assay − Efficacy/safety
CNTO1275CRD 3003	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in patients with moderately to severely active Crohn's disease (n=1281) induced into clinical response with ustekinumab in the induction studies, CRD3001 and CRD3002	Maintenance (staring from Week 8 following IV induction): Placebo, 90 mg SC q12w, or 90 mg SC q8w	− PK: descriptive, PopPK; samples analyzed using ECLIA assay − PD − Immunogenicity: samples analyzed using ECLIA assay − Efficacy/safety

Figure 1. Ustekinumab clinical development program for CD
(Source: Figure 1 of Module 2.5 Clinical Overview)



2.2 General Attributes of the Drug

2.2.1 Is the product currently marketed in US and what are the indications? What formulations of the drug product are approved?

Ustekinumab (Stelara®) is currently marketed in the US. It was approved in the United States (US) on September 25, 2009 under BLA 125261 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. It was also approved in the US on September 20, 2013 for the treatment of adults with active psoriatic arthritis (PsA).

Ustekinumab is currently approved as 45 mg/0.5 mL and 90 mg/mL solution in prefilled syringe presentation for SC injection in the US.

2.2.2 What is the new proposed formulation of the drug product?

A new 5 mg/mL (130 mg/26 mL vial) liquid-in-vial (LIV) formulation is proposed for use as an IV induction therapy for CD.

The proposed drug product is supplied as a single-use sterile solution, designed to deliver 130 mg of ustekinumab, in a 30 mL, Type-1 glass vial for IV. The target composition is 5 mg/mL ustekinumab, with nominal excipient concentrations of (b) (4) L-histidine, (b) (4) sucrose, (b) (4) polysorbate 80, (b) (4) methionine, and (b) (4) EDTA disodium salt dihydrate at pH (b) (4)

2.2.3 What are the proposed therapeutic indication and the mechanism of action?

The proposed indication is for the treatment of adult patients [redacted] (b) (4) with moderately to severely active CD who have:

- Failed or were intolerant to immunomodulators or corticosteroids, but never failed [redacted] (b) (4) or
- Failed or were intolerant to one or more [redacted] (b) (4)

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds the p40 subunit common to the heterodimeric cytokines IL-12 and IL-23. It neutralizes the biological activities of IL-12 and IL-23 by preventing these cytokines from binding to their shared cell-surface receptor chain, IL IL-12Rβ1 (IL-12 receptor beta-1), expressed on the surface of immune cells.

2.2.4 What are the proposed dosing regimens and route of administration?

The proposed dosing regimens for the CD indication are:

[redacted] (b) (4)

Although the Applicant proposed to include [redacted] (b) (4) the Clinical Pharmacology Review team does not agree with the proposal. See further discussions in Section 2.4.1.3.

2.2.5 What drug products are approved for the same indication in the US?

Currently, two classes of antibodies are approved for the CD indication in US. These include the anti-TNFα antibodies adalimumab, infliximab, and certolizumab pegol, and the integrin blocking antibodies natalizumab and vedolizumab

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology studies and the clinical studies used to support dosing or claims?

2.3.1.1. Phase 1

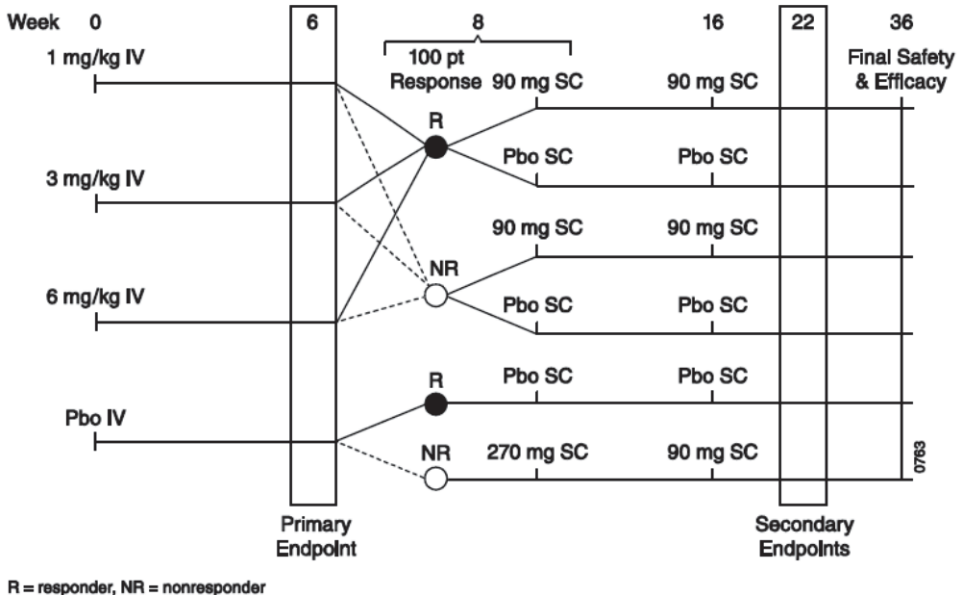
The phase 1 study NAP1002 was a randomized, open-label, parallel-design study to compare the single-dose PK of IV ustekinumab delivered in two different LIV formulations, 90 mg/mL and 5 mg/mL (130 mg/26 mL), in healthy subjects. The 90 mg/mL is the currently approved formulation used for SC injection, and it was used for IV infusion in the phase 3 induction trials in CD patients. The 5 mg/mL is the newly developed to-be-marketed formulation for IV infusion.

2.3.1.2 Phase 2

The phase 2a study C0379T07 was a proof-of-concept study to evaluate IV and SC induction doses of ustekinumab for the treatment of CD. This small multicenter, randomized study examined 2 regimens of ustekinumab induction therapy, either a single 4.5 mg/kg IV dose at Week 0 or 90 mg SC at Weeks 0, 1, 2, and 3, in adult subjects with moderately to severely active CD who failed or were intolerant to immunomodulators or corticosteroids, but never failed anti-TNFα treatment.

The phase 2b study C0743T26 was a multicenter, randomized, double-blind study of ustekinumab IV induction followed by SC maintenance in subjects with moderately to severely active CD who had previously failed or were intolerant to one or more TNFα antagonist therapy. Three different doses of single ustekinumab administration (1, 3, and 6 mg/kg IV) were evaluated in inducing clinical remission and to obtain data to support the selection of a maintenance dose regimen for continued clinical development. Figure 2 depicts the overall study schema of C0743T26.

Figure 2. Study schema of C0743T26
(Source: Figure 1 of Module 2.7.3 Summary of Clinical Efficacy)

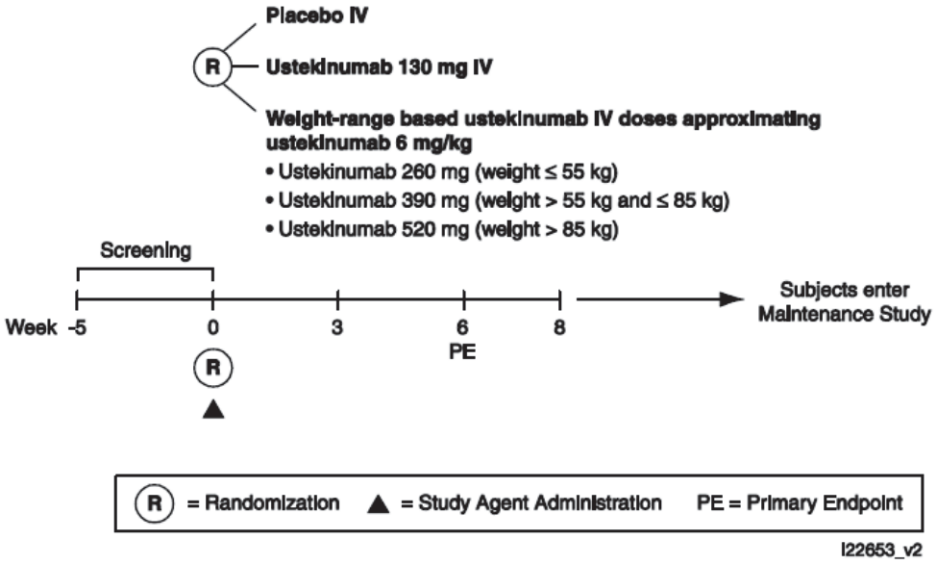


2.3.1.3 Phase 3 Induction Studies

The two phase 3 studies CRD3001 and CRD3002 were randomized, double-blind, placebo-controlled, parallel-group, multicenter studies to evaluate the efficacy and safety of a single IV administration of ustekinumab as an induction therapy in achieving clinical response at Week 6 in patients with moderately and severely active CD.

The design (shown in Figure 3) of the two studies was essentially identical with the exception of the subject population. In study CRD3001, subjects must have failed or were intolerant to TNFα antagonists (i.e., infliximab, adalimumab, or certolizumab pegol) at a dose approved for the treatment of CD. Study CRD3002 included subjects with evidence of active inflammation who had failed conventional therapy (i.e., immunomodulators and/or corticosteroids).

Figure 3. Study schema for induction studies CRD3001 and CRD3002
(Source: Figure 1 of Module 2.7.3 Summary of Clinical Efficacy)



2.3.1.4 Phase 3 Maintenance Study

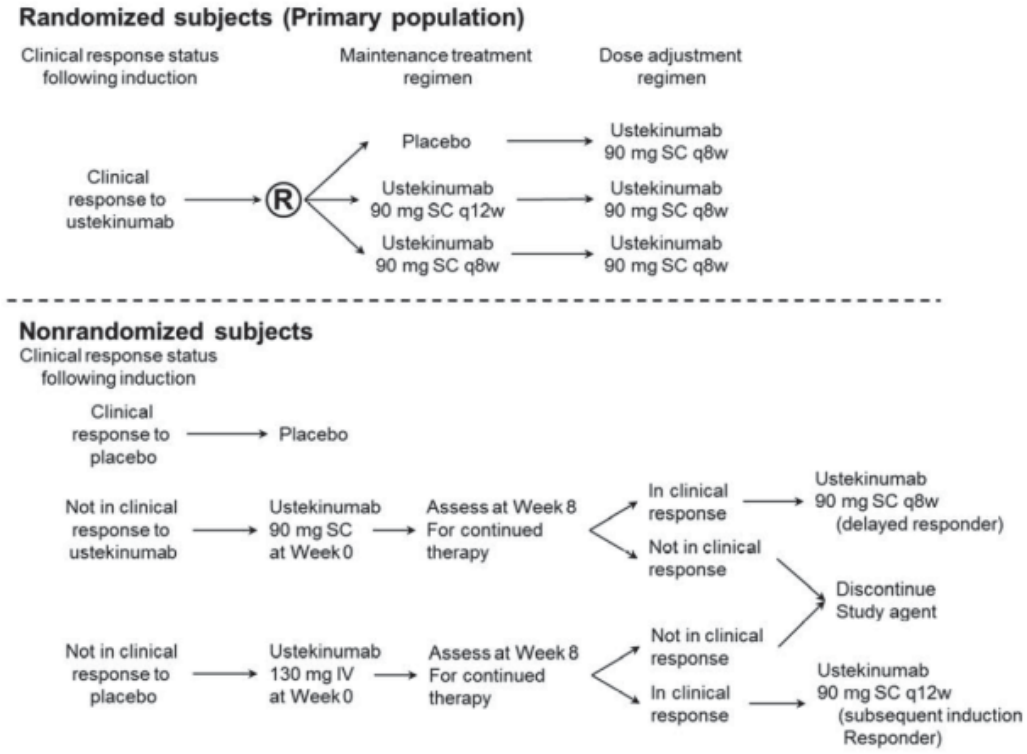
The phase 3 study CRD3003 was a multicenter, placebo-controlled, parallel-group, double-blind, randomized withdrawal study to evaluate the safety and efficacy of SC regimens of ustekinumab maintenance therapy in subjects with moderately to severely active CD who were induced into clinical response with IV ustekinumab. The maintenance portion of the study was through Week 44 and the data were included in this BLA. A subsequent study extension continues up to Week 272 for eligible subjects.

Subjects in the primary population (i.e., those achieved clinical response with IV ustekinumab at Week 8 of either the CRD3001 or CRD3002 induction studies) were randomized at Week 0 of the maintenance study to one of three treatment groups as presented in Figure 4, i.e., placebo, 90 mg SC q12w, or 90 mg SC q8w. Randomized subjects who subsequently met the loss of clinical response (LOR) criteria at any time between Week 8 and Week 32 of the study were eligible to have a single dose adjustment to ustekinumab 90 mg SC q8w. Subjects who had a dose

adjustment were evaluated 16 weeks after adjustment and were discontinued from study agent if not in clinical response.

Subjects in the other populations (i.e., those in clinical response to placebo, not in clinical response to placebo or ustekinumab) were not randomized and were assigned treatment as shown in Figure 4.

Figure 4. Maintenance study populations and their respective treatment groups
(Source: Figure 3 of Module 2.7.3 Summary of Clinical Efficacy)



2.3.2 What are the clinical endpoints and how are they defined in the clinical pharmacology studies?

The Crohn's Disease Activity Index (CDAI) was used as the primary tool for assessing disease activity response to ustekinumab in the phase 3 trials. The CDAI contains information on eight different CD-related variables: extraintestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid stools, abdominal pain/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being. The last 4 variables are scored over 7 days by the subject on a diary card.

2.3.2.1 Induction

The primary endpoint for the induction studies CRD3001 and CRD 3002 is 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 are considered to be in clinical response if a CDAI score of < 150 is attained.

The major secondary endpoints, in order of importance, are:

1. Clinical remission at Week 8, defined as a CDAI score of < 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

Other secondary tools for assessment included CRP concentration, fecal lactoferrin and calprotectin, the well-being questionnaires Inflammatory Bowel Disease Questionnaire (IBDQ) and the 36-Item Short Form Health Survey (SF-36), fistula assessment, pyoderma gangrenosum assessment, and mucosal healing.

2.3.2.1 Maintenance

The primary endpoint for CRD 3003 was clinical remission at Week 44. Clinical remission was defined as a CDAI score of <150 points. Subjects who had any of the following events prior to Week 44 were not considered to be in clinical remission for the primary endpoint analysis, regardless of the actual CDAI score:

- A CD-related surgery due to lack of efficacy of study agent
- Discontinuation of study agent due to lack of efficacy or due to an AE of worsening CD
- LOR, defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the Week 0 CDAI score (i.e., Week 8 in the induction study CRD3001 or CRD3002), which was assessed between Week 8 and Week 32
- Specified changes in concomitant CD medications

In addition, subjects who did not return for evaluation or had insufficient data to assess their clinical remission status at Week 44 (i.e., <4 components of the CDAI are available) were also considered to not have achieved clinical remission.

2.3.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic (PK) parameters and exposure response relationships?

Yes, the active moiety which is the actual therapeutic protein was measured to assess the PK parameters and E-R relationships.

Ustekinumab concentration was determined by two bioanalytical methods: an enzyme-linked immunosorbent assay (ELISA) and an electrochemiluminescent immunoassay (ECLIA) method on the Meso Scale Discovery (MSD®) platform (Gaithersburg, MD, USA) (see Section 2.9.1).

2.4 Dose-Response (D-R) and Exposure-Response (E-R)

2.4.1 What are the characteristics of the D-R and E-R relationships for efficacy?

There were dose-dependent and concentration-dependent increases in clinical efficacy of ustekinumab for both the induction dose and the maintenance dosing regimen.

For the induction dose, higher proportions of subjects achieved clinical remission at Week 8 in the ~6 mg/kg IV dose group than the 130 mg IV dose group, in subjects who have or have not failed TNFα antagonist. The clinical remission rate of the ~6 mg/kg and 130 mg dose group was significantly higher than that of the placebo group for both patient populations (Table 2).

For the maintenance dosing regimen, the proportion of subjects who achieved clinical remission at Week 44 was higher in the 90 mg/kg SC q8w group than the 90 mg SC q12w group for subjects who have or have not failed previous TNFα antagonist. The clinical remission rate at Week 44 in the 90 mg SC q8w group was significantly higher than that in the placebo group for the TNFα antagonist failure population but not for the TNFα antagonist failure population. Nonetheless, the study was not powered to detect the difference in clinical remission rate between subjects who have and have not failed TNFα antagonist (Table 2).

Results from E-R analysis showed that clinical remission rate at Week 8 during induction was near the plateau at ustekinuamb concentrations in the range of 5 – 10 μg/mL in subjects who have or have not failed TNFα antagonist, whereas during maintenance therapy a plateau was reached at ustekinumab concentrations in the range of 2 – 5 μg/mL in subjects who have not failed TNFα antagonist. There was no E-R relationship for maintenance therapy in subjects who have failed TNFα antagonist.

2.4.1.1 D-R and E-R relationships for efficacy in the induction phase

Table 2 summarizes the responses for the primary endpoint (i.e., clinical response at Week 6) and the major secondary endpoint (clinical remission at Week 8) for subjects who have previously failed TNFα antagonist (i.e., in CRD3001) and subjects who have not failed TNFα antagonist (i.e., in CRD3002). Overall, a D-R relationship was observed in the clinical response at Week 6 for subjects who have not failed TNFα antagonist as well as the clinical remission at Week 8 for subjects who have or have not failed TNFα antagonist. The response rates increased as the dose increased from the 130 mg to ~ 6 mg/kg ustekinumab IV induction dose.

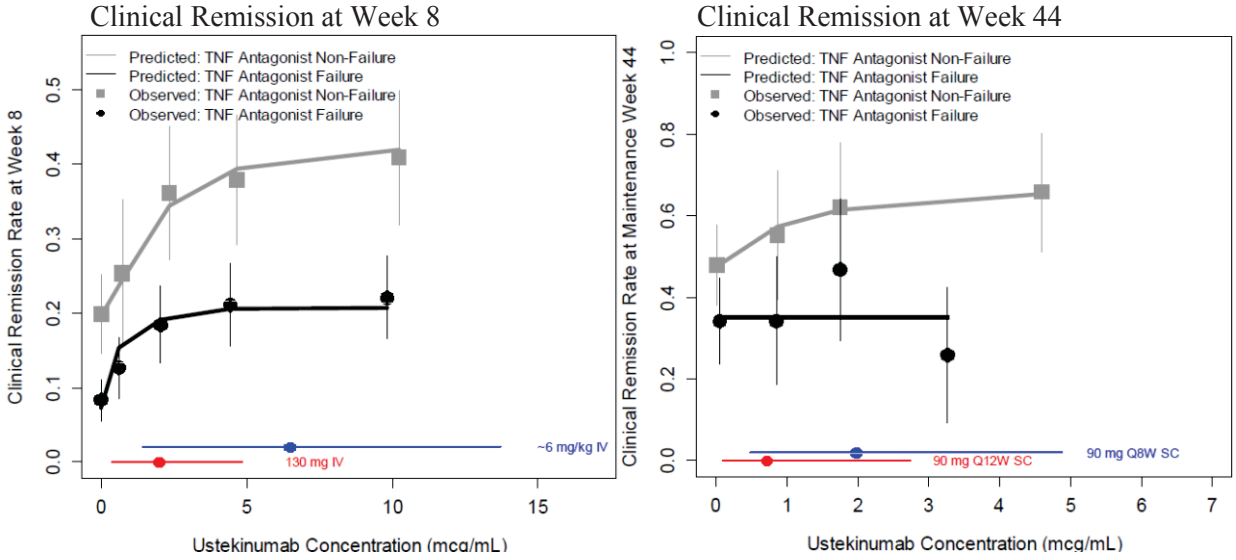
The Applicant also explored the relationship between ustekinumab exposure and response using a logistic regression modeling approach. As demonstrated in Figure 5 left panel, the probability of clinical remission at Week 8 increased rapidly as concentration increased from 0 to 5 μg/mL and approached a plateau at 5 – 10 μg/mL concentration range. Subjects who have not failed a TNFα antagonist consistently achieved higher remission rates at a given concentration than subjects who have previously failed a TNFα antagonist. Compared with the 130 mg dose, the model showed that the ~6 mg/kg dose can achieve systemic exposure that spans the portion of the E-R curve associated with the highest remission rates at Week 8 in TNFα antagonist non-failure subjects.

Table 2. Response summary for the primary endpoint (CRD3001, CRD3002, and CRD3003) and major secondary endpoint (CRD3001, CRD3002) in the induction phase and maintenance phase
(Source: combined data from Tables 6 and 7 of CRD3001 CSR, Tables 6 and 7 of CRD3002 CSR, and TEFCREM13B of CRD3003 CSR)

Patient population	TNFα Antagonist Failure			TNFα Antagonist Non Failure		
Induction Study	CRD3001			CRD3002		
Dose group (IV infusion)	Placebo	130 mg	~ 6 mg/kg	Placebo	130 mg	~ 6 mg/kg
Proportion of subjects in clinical response at Week 6 (%)	53/247 (21.5)	84/245 (34.3)	84/249 (33.7)	60/209 (28.7)	108/209 (51.7)	116/209 (55.5)
p-value*		0.002	0.003		<0.001	<0.001
Proportion of subjects in clinical remission at Week 8 (%)	18/247 (7.3)	39/245 (15.9)	52/249 (20.9)	41/209 (19.6)	64/209 (30.6)	84/209 (40.2)
p-value*		<0.001	0.003		0.009	<0.001
Maintenance Study	CRD3003					
Dose group (SC injection)	Placebo	90 mg q12w	90 mg q8w	Placebo	90 mg q12w	90 mg q8w
Proportion of subjects (%) in clinical remission at Week 44	16/61 (26.2)	22/57 (38.6)	23/56 (41.1)	31/70 (44.3)	41/72 (56.9)	45/72 (62.5)
p-value*		0.140	0.102		0.146	0.020

*Compared to placebo

Figure 5. Goodness-of-fit plot for E-R model in induction phase (left panel) and the maintenance phase (right panel)
(Source: Figures 1 and 3 of Exposure-Response Analyses for Efficacy. Of Note, the induction data were from three studies, C0743T26, CRD3001, and CRD3002, the maintenance data were from Study CRD3003.)



2.4.1.2 D-R and E-R relationships for efficacy in the maintenance phase

A dose-dependent response was observed for the primary endpoint (i.e., clinical remission at Week 44) in the maintenance phase; the proportion of subjects in clinical remission at Week 44 was higher in the 90 mg SC q8w than that in the 90 mg SC q12w group (53.1% vs. 48.8%, Table

3). The clinical remission rate in these two treatment groups was significantly higher than that in the placebo group (35.9%, p = 0.005 and 0.04, respectively).

A subgroup analysis based on previous experience with TNFα antagonist showed similar dose-dependent response in subjects who have or have not failed TNFα antagonist (Table 2). The clinical remission rate at Week 44 was higher in the two ustekinumab treatment groups compared with that in the placebo group (38.6% and 41.1% vs. 26.2% in subjects who have failed TNFα antagonist, and 56.9% and 62.5% vs. 44.3% in subjects who have not failed TNFα antagonist). Of note, the difference in clinical remission rate was not statistically different between the treatment groups and placebo group in TNFα failure subjects, but the study was not powered to detect such differences among different dose groups in either the TNFα failure population or TNFα non-failure population alone.

Table 3. Number of randomized subjects in clinical remission at Week 44
(Source: Table 5 of CRD3003 CSR)

		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.

[TEFCREM01A.rtf] [CNTO1275\CRD3003\DBR CSR\RE CSR\tefcrem01a.sas] 07OCT2015, 17:57

An E-R relationship was established in subjects who have not failed TNFα antagonist in the maintenance phase. The probability of clinical remission at Week 44 increased as concentration increased from 0 to 2 µg/mL and reached a plateau at concentration range of 2 - 5 µg/mL (Figure 5 right panel). Compared with the 90 SC q12w regimen, the model predicted that the 90 SC q8w can achieve higher exposure which covers the portion of E-R curve associated with slightly higher remission rates at Week 44. No E-R relationship was observed in subjects who have failed TNFα antagonist.

2.4.1.3 Efficacy in subjects who had a dose adjustment in the maintenance phase

In Study CRD3003, randomized subjects who met LOR criteria at any time between Week 8 and Week 32 were eligible to have a single dose adjustment to ustekinumab 90 mg SC q8w. Among subjects who were randomized to ustekinumab 90 mg SC q12w, met LOR criteria, and had a dose adjustment to 90 mg SC q8w, approximately 40% achieved clinical remission 16 weeks later, compared with 32% remission rate in subjects in the ustekinumab 90mg SC q8w who met LOR criteria and remained on the 90 mg SC q8w regimen. The ~8% improvement in clinical

remission by increasing dosing frequency from q12w to q8w in subjects who lost response over subjects without dose adjustment suggested that the 90 mg SC q8w was more effective in achieving clinical remission than the 90 mg SC q12w.

Among the 133 subjects randomized to the placebo group, 51 subjects had a dose adjustment to ustekinumab 90 mg SC q8w after meeting LOR criteria. Twenty-nine of 132 subjects randomized to the ustekinumab 90 mg SC q12w group had a dose adjustment to ustekinumab 90 mg SC q8w after meeting LOR criteria; 28 of 131 subjects randomized to the ustekinumab 90 mg SC q8w group met LOR criteria for dose adjustment but continued to receive ustekinumab 90 mg q8w per protocol. The response of these subjects 16 weeks after the dose adjustment was summarized in Table 4.

Table 4. Summary of Response at 16 weeks after dose adjustment in subjects who experienced loss of response

	Dose Adjustment		
	Placebo SC → 90 mg SC q8w	90 mg SC q12w → 90 mg SC q8w	90 mg SC q8w → 90 mg SC q8w
No. randomized subjects	133	132	131
No. subjects who met LOR and had a dose adjustment	51	29	28
Response 16 weeks after dose adjustment			
Clinical remission	39.2%	41.1%	32.1%
Clinical response	70.6%	55.2%	46.4%

2.4.2 What are the characteristics of the D-R and E-R relationships for safety?

2.4.2.1 D-R and E-R relationships for safety in the induction phase

Overall results from CRD3001 and CRD 3002 showed that the incidence of safety events appeared similar between the 130 mg and ~6 mg/kg dose groups in the induction phase (Table 5 and Table 6). There was a slightly higher occurrence of SAEs and serious infections in the ~6 mg/kg dose group than the 130 mg dose group in CRD3001 (i.e., TNFα antagonist failure subjects), but the trend was not observed in CRD3002 (i.e., TNFα antagonist non-failure subjects).

No relationship between ustekinumab exposure and the safety events (i.e., infections, serious infections, SAEs) were observed for induction at the dose levels evaluated in C0743T26, CRD3001, and CRD3002. The incidence of these safety events appeared similar across the serum ustekinumab concentration quartiles during induction (Table 7).

Table 5. Summary of key safety findings through Week 8 in CRD3001; treated subjects excluding those enrolled prior to Study re-start
(Source: Table 11 of CRD3001 CSR)

Table 11: Summary of Key Safety Findings through Week 8; Treated Subjects Excluding Those Enrolled Prior to Study Re-start

		Ustekinumab		
	Placebo	130 mg	6 mg/kg	Combined
Analysis set: Treated subjects excluding those enrolled prior to study re-start	245	246	249	495
Average duration of follow-up (weeks)	7.85	7.89	7.79	7.84
Average exposure (number of administrations)	1.00	1.00	1.00	1.00
Subjects who died	0	0	0	0
Subjects with 1 or more				
Adverse events	159 (64.9%)	159 (64.6%)	164 (65.9%)	323 (65.3%)
Serious adverse events	15 (6.1%)	12 (4.9%)	18 (7.2%)	30 (6.1%)
Infections[a]	58 (23.7%)	57 (23.2%)	64 (25.7%)	121 (24.4%)
Serious infections[a]	3 (1.2%)	3 (1.2%)	7 (2.8%)	10 (2.0%)
Infusion reactions (AEs temporally associated with infusion)	5 (2.0%)	11 (4.5%)	9 (3.6%)	20 (4.0%)

[a] Infection as assessed by the investigator.

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Table 6. Summary of key safety findings through Week 8 in CRD3002; treated subjects excluding those enrolled prior to Study re-start
(Source: Table 12 of CRD3002 CSR)

		Ustekinumab		
	Placebo	130 mg	6 mg/kg	Combined
Analysis set: Treated subjects excluding those enrolled prior to study re-start	208	212	207	419
Average duration of follow-up (weeks)	7.88	7.89	7.88	7.88
Average exposure (number of administrations)	1.00	1.00	1.00	1.00
Subjects who died	0	0	0	0
Total number of subjects with treatment-emergent				
Adverse events	113 (54.3%)	106 (50.0%)	115 (55.6%)	221 (52.7%)
Serious adverse events	12 (5.8%)	10 (4.7%)	6 (2.9%)	16 (3.8%)
Infections[a]	48 (23.1%)	31 (14.6%)	45 (21.7%)	76 (18.1%)
Serious Infections[a]	3 (1.4%)	3 (1.4%)	1 (0.5%)	4 (1.0%)
Infusion reactions (AEs temporally associated with infusion)	6 (2.9%)	5 (2.4%)	3 (1.4%)	8 (1.9%)

[a] Infection as assessed by the investigator.

Adapted from [TSFAE11.rtf] [CNTO1275\CRD3002\DBR_W20\RE_W20\tsfae11.sas] 26NOV2014, 16:49

Table 7. Number of subjects with 1 or more treatment-emergent infections, serious Infections, and serious adverse events by serum ustekinumab concentrations quartiles; treated subjects in the induction phase of C0743T26 and treated subjects in CRD3001 and CRD3002 excluding those enrolled prior to study re-start
(Source: Table 17 of Module 2.7.2 Summary of Clinical Pharmacology Studies)

	Treatment Emergent Events (N, %) in Induction Phase Through Week 8 (C0743T26/CRD3001/CRD3002)				
Serum ustekinumab concentration at Week 8 by quartile[a]	Placebo IV[b]	Q1	Q2	Q3	Q4
No evaluable subjects	585	228	227	228	227
Subjects with 1 or more treatment-emergent infections[c]	138 (23.6%)	46 (20.2%)	44 (19.4%)	57 (25.0%)	51 (22.5%)
Subjects with 1 or more serious infections[c]	7 (1.2%)	1 (0.4%)	0 (0%)	4 (1.8%)	3 (1.3%)
Subjects with 1 or more serious adverse events	38 (6.5%)	10 (4.4%)	9 (4.0%)	9 (3.9%)	6 (2.6%)

Q1=≤ 1st Quartile; Q2=>1st and ≤ 2nd Quartile; Q3=>2nd and ≤ 3rd Quartile; Q4=>3rd Quartile
[a]1st quartile=1.38 µg/mL, 2nd quartile=3.20 µg/mL, 3rd quartile=6.60 µg/mL are based on subjects in ustekinumab 1 mg/kg, 3 mg/kg, 6 mg/kg, and 130 mg combined group.
[b]Subjects randomized to placebo in C0743T26, CRD3001, and CRD3002.
[c]Infection as assessed by the investigator.

2.4.2.2 D-R and E-R relationships for safety in the maintenance phase

There appears to be a slightly higher incidence of serious infections in the ustekinumab 90 mg SC q12w group than the ustekinumab 90 mg SC q8w during the maintenance phase up to the point of dose adjustment. While the number of serious infections was small and the duration of follow up was short, this finding should be taken into consideration when comparing the two dosing regimens.

During the maintenance phase (up to the point of dose adjustment) in study CRD3003, the proportions of randomized subjects with serious infections were slightly higher in the ustekinumab 90 mg SC q12w group. Specifically, 2.3% (3 of 133 subjects) in the placebo group, 5.3% (7 of 132 subjects) in the ustekinumab 90 mg SC q12w group, and 2.3% (3 of 131 subjects) in the ustekinumab 90 mg SC q8w group.

The incidence was also analyzed with adjustment for the differences in duration of follow up due to dose adjustment. The number of serious infections per hundred subject-years of follow up prior to the dose adjustment was 9.68 and 3.38 for the ustekinumab 90 mg SC q12w and 90 mg SC q8w, respectively, with the incidence in the ustekinumab 90 mg SC q8w group being similar to that of the placebo group (Table 8). However, the number of serious infections per hundred subject-years of follow up after the dose adjustment was 6.64 and 13.68 for the ustekinumab 90 mg SC q12w and 90 mg SC q8w, respectively, compared to 3.94 in the placebo group.

The Applicant stated the adjusted incidence can be a very useful strategy when the total subject years of follow-up are substantial, but the analysis can also create an appearance of high incidences (or differences in incidence) particularly where the total subject years of follow-up is short, as presented in Table 8. See the Applicant's response to the FDA's IR dated May 10,

2016 for more information (SDN 20; June 3, 2016). Nonetheless, because serious infection could be a concern for CD patients receiving ustekinumab, the information from this safety finding should be taken into consideration when comparing the two maintenance dosing regimens.

Table 8. Number of serious adverse events per hundred subject-years of follow up through Week 44 by MedDRA system-organ class and preferred terms; treated subjects who were randomized
(Source: Data rearranged from Appendix TSFAE04D of CRD3003 CSR)

	Data up to the time of meeting loss of response criteria for dose adjustment			Data from the time of meeting loss of response criteria for dose adjustment onward		
	Placebo SC	90 mg SC q12w	90 mg SC q8w	Placebo SC → 90 mg SC q8w	90 mg SC q12w → 90 mg SC q8w	90 mg SC q8w → 90 mg SC q8w
No. Subjects	133	132	131	51	29	29
Average duration of follow up (weeks)	32.0	36.6	35.2	25.9	27.0	26.2
Total subject-years of follow up	81.8	93.0	88.7	25.4	15.1	14.6
No. serious adverse events per hundred subject-years of follow up						
Total	24.46	21.51	18.03	35.43	46.46	47.89
Infections and infestations	3.67	9.68	3.38	3.94	6.64	13.68

Overall, no relationship between ustekinumab exposure and the safety events (i.e., infections, serious infections, SAEs) were observed for maintenance at the dose levels evaluated in CRD3003. The incidence of the safety events appeared similar across the serum ustekinumab concentration quartiles (Table 9).

Table 9. Number of subjects with 1 or more treatment-emergent infections, serious infections, and serious adverse events by serum ustekinumab concentrations quartiles; treated subjects who were randomized in CRD3003
(Source: Table 17 of Module 2.7.2 Summary of Clinical Pharmacology Studies)

	Treatment Emergent Events (N, %) in Maintenance Phase Through Week 8 (CRD3003)				
Average trough ustekinumab concentration quantile[a,b]	Placebo SC[c]	Q1	Q2	Q3	Q4
No evaluable subjects	133	49	48	49	48
Subjects with 1 or more treatment-emergent infections[d]	66 (49.6%)	27 (55.1%)	18 (37.5%)	30 (61.2%)	24 (50.0%)
Subjects with 1 or more serious infections[d]	3 (2.3%)	3 (6.1%)	2 (4.2%)	1 (2.0%)	2 (4.2%)
Subjects with 1 or more serious adverse events	20 (15.0%)	5 (10.2%)	7 (14.6%)	1 (2.0%)	5 (10.4%)

Q1=≤ 1st Quartile; Q2=>1st and ≤ 2nd Quartile; Q3=>2nd and ≤ 3rd Quartile; Q4=>3rd Quartile
[a]1st quartile=0.50 µg/mL, 2nd quartile=1.14 µg/mL, 3rd quartile=2.29 µg/mL are based on subjects who were randomized and received ustekinumab 90 mg SC during the maintenance study.
[b]For randomized subjects who received ustekinumab 90 mg SC q12w on entry of the maintenance study, serum trough ustekinumab concentrations on Weeks 24 and 36 are averaged; for randomized subjects who received ustekinumab 90 mg SC q8w during the maintenance study, serum trough ustekinumab concentrations on Weeks 24, 32, and 40 are averaged.
[c]Subjects randomized to placebo in CRD3003; includes data up to dose adjustment due to meeting loss of response criteria.
[d]Infection as assessed by the investigator.

2.4.3 Is the dose and dosing regimen selected consistent with the known D-R/E-R relationship?

The Applicant's proposed dosing regimen for induction is a single IV infusion dose of ustekinumab using three weight-based tiers of approximately 6 mg/kg (Section 2.2.4). This proposed induction dose is acceptable because it is consistent with the D-R and E-R relationships as described in Sections 2.4.1 and 2.4.2.

For the maintenance treatment, the Applicant's proposal of 90 mg SC q8w is acceptabl (b) (4)

As described in Section 2.4.1, the proposal of the 90 mg SC q8w is supported by the numerically higher proportion of subjects who achieved clinical remission at Week 44 in the 90 mg SC q8w group compared with the 90 mg SC q12w group (53.1% vs. 48.8%); remission rate from both regimens was greater than that in the placebo group (35.9%). In addition, a lower serious infection rate was observed in the 90 mg SC q8w group than the 90 mg SC q12w group (see Section 2.4.2).

(b) (4)

2.5 What are the PK characteristics of the drug?

Ustekinumab PK have been characterized in psoriasis patients in BLA 125261, and the corresponding PK information has been included in the current labeling. Described below is the information about ustekinumab PK characteristics in patients with CD included in this BLA 761044.

2.5.1 What are the PK parameters of ustekinumab in healthy adults?

Ustekinumab PK following a single IV administration of 6 mg/kg were evaluated for the two LIV formulations (i.e., 90 mg/mL LIV and 5 mg/mL LIV formulations) in healthy adults in Study NAP1002 (see Section 2.8 for more information about the different formulations). PK parameter estimates derived from the noncompartmental analysis (NCA) of the concentration-time profiles are summarized in Table 10.

Table 10. Summary of ustekinumab PK parameter estimates in healthy adults
(Source: Table 3 of NAP1002 CSR)

	Ustekinumab 6 mg/kg	
	90 mg/mL LIV formulation	5 mg/mL LIV formulation
Subjects evaluable	70	69
C_{max} (µg/mL)		
N	69	69
Mean (SD)	199.105 (22.7180)	193.204 (27.0651)
Median	200.650	196.730
GeoMean	197.826	191.296
CV (%)	11.410	14.009
Range	(158.65; 250.91)	(133.09; 246.77)
AUC_{last} (day*µg/mL)		
N	67	69
Mean (SD)	3051.585 (542.2735)	2969.654 (573.6627)
Median	3132.000	2929.550
GeoMean	3003.726	2915.752
CV (%)	17.770	19.317
Range	(1840.77; 4688.34)	(1864.07; 4471.86)
AUC_{inf} (day*µg/mL)		
N	68	68
Mean (SD)	3218.279 (661.0879)	3132.429 (690.2049)
Median	3268.115	3031.290
GeoMean	3152.088	3059.822
CV (%)	20.542	22.034
Range	(1849.46; 5170.62)	(1887.09; 5034.76)
$T_{1/2}$ (day)		
N	69	68
Mean (SD)	25.091 (6.0573)	24.698 (6.1909)
Median	24.650	23.960
CV (%)	24.141	25.066
Range	(14.41; 38.92)	(11.68; 40.78)
CL (mL/day)[a]		
N	69	68
Mean (SD)	136.311 (33.4437)	143.076 (36.6033)
Median	128.300	137.770
CV (%)	24.535	25.583
Range	(81.46; 234.93)	(83.54; 243.49)
CL (mL/kg/day)[a]		
N	69	68
Mean (SD)	1.947 (0.4089)	2.007 (0.4355)
Median	1.840	1.980
CV (%)	21.002	21.699
Range	(1.16; 3.24)	(1.19; 3.18)
V_z (mL)[a]		
N	69	68
Mean (SD)	4720.952 (772.0429)	4861.433 (868.2170)
Median	4665.120	4677.555
CV (%)	16.354	17.859
Range	(2846.49; 7266.49)	(3330.45; 7104.89)
V_z (mL/kg)[a]		
N	69	68
Mean (SD)	67.700 (9.4996)	68.393 (9.7334)
Median	66.800	67.520
CV (%)	14.032	14.232
Range	(46.13; 91.40)	(44.55; 91.46)

[a]Body weight adjusted value

2.5.2 What are Population PK parameters of ustekinumab in patients with CD?

Using concentration data from Studies 0743T26, CRD3001, CRD3002, and CRD3003, ustekinumab PopPK were characterized by a two-compartment model with first-order absorption in patients with CD.

The typical value of ustekinumab CL in a subject weighing approximately 70 kg was 0.191 L/day (95% CI: 0.185 to 0.197 L/day), V2 was 2.74 L (95% CI: 2.69 to 2.78 L). The estimated

bioavailability of ustekinumab following SC administration was 78.3% while the median terminal elimination half-life of was approximately 19 days.

2.5.3 How does the PK of ustekinumab in healthy adults compare to that in patients with CD?

Following 6 mg/kg IV ustekinumab, the median serum ustekinumab concentration at corresponding timepoints were more than 2-fold higher in healthy adults from the NAP1002 study than in CD patients from the combined CRD3001/CRD3002 studies (Table 11). Despite similar median body weight between subjects in the NAP1002 study (70.1 kg) and those in the combined CRD3001/3002 studies (69.0 kg), the Applicant could not identified the reason for the differences in concentrations.

The Applicant also compared the ustekinumab PK parameters from NCA in healthy subjects with those obtained from PopPK analysis in CD subjects. As summarized in Table 12, the volume of distribution was similar between healthy subjects with CD patients, but the clearance was lower (0.14 vs. 0.19 L/day) and the half-life was longer (24.0 vs. 18.9 days) in healthy subjects compared with CD patients.

Table 11. Summary of serum ustekinumab concentrations in healthy subjects who received 6 mg/kg IV in Study NAP1002 and CD patients who received doses of ~6 mg/kg IV in the combined Phase 3 studies CRD3001 and CRD3002
(Source: Table 7 of Module 2.7.2 Summary of Clinical Pharmacology Studies)

	Ustekinumab 6 mg/kg	
	CNTO1275NAP1002[a]	Combined[b] CRD3001 & CRD3002
Subjects treated	70	456
Day 1, pre-administration		
N	69	454
Mean (SD)	0.0343 (0.13240)	0.44 (5.806)
Median	0.0000	0.00
IQ range	(0.0000; 0.0000)	(0.00; 0.00)
Range	(0.000; 0.708)	(0.0; 109.8)
Day 1, 0.5 hr (NAP) / 1 hr (CRD) post-infusion		
N	69	440
Mean (SD)	199.0844 (22.71149)	125.20 (33.634)
Median	200.6540	126.06
IQ range	(183.2195; 212.4501)	(106.07; 146.16)
Range	(158.651; 250.909)	(0.0; 224.8)
Week 3		
N	68	420
Mean (SD)	45.8641 (7.88238)	25.17 (10.587)
Median	47.1191	24.50
IQ range	(40.4226; 50.3958)	(17.38; 32.53)
Range	(28.771; 70.297)	(0.0; 72.7)
Week 6		
N	68	398
Mean (SD)	23.8977 (6.49704)	11.12 (6.588)
Median	24.5350	9.96
IQ range	(19.1397; 27.8201)	(6.77; 15.16)
Range	(10.014; 42.747)	(0.0; 45.0)

Week 8		
N	68	307
Mean (SD)	16.7960 (5.78890)	6.94 (4.543)
Median	17.3535	6.36
IQ range	(12.7137; 20.0336)	(3.40; 9.58)
Range	(4.396; 30.638)	(0.0; 24.8)

Key: IQ=interquartile; SD=standard deviation.
[a] 90 mg/mL LIV formulation.
[b] 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). Analysis set: Subjects treated with ustekinumab in CNTO1275CRD3001 and CNTO1275CRD3002 excluding those enrolled prior to study re-start.

Table 12. Ustekinumab PK parameters in healthy subjects and in CD patients
(Source: Table 8 of Module 2.7.2 Summary of Clinical Pharmacology Studies)

	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.

2.5.4 What is the inter-subject variability of the PK parameters in patients with CD?

The inter-subject variability for the estimated PopPK parameters CL, V2, V3, and ka were 29.1%, 14.7%, 32.2%, and 72.1%, respectively in CD patients receiving ustekinumab.

2.5.5 What are the characteristics of drug absorption, distribution, and elimination?

Absorption: The bioavailability following SC ustekinumab administration in patients with CD was estimated to be 78.3% as described in Section 2.5.2.

Distribution: The Pop-PK estimates for the central (V2) and peripheral (V3) volumes of distribution (and 95% CI) in CD patients with an approximate body weight of 70 kg were 2.74 (2.69, 2.78) L and 1.88 (1.66, 2.13) L, respectively. These results indicate that ustekinumab primarily distributed in the intravascular space, with limited distribution to the extravascular space.

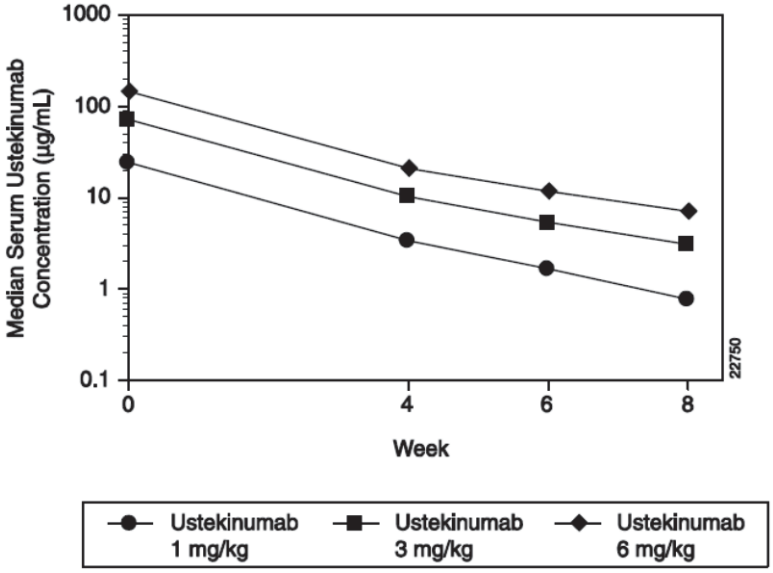
Elimination: The typical value of the terminal elimination half-life of ustekinumab in patients with CD was approximately 19 days.

2.5.6 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

After a single IV administration of ustekinumab at doses of 1, 3, or 6 mg/kg during induction phase in the Phase 2 study C0743T26 (n = 526), the median serum ustekinumab concentrations

in all treated subjects were approximately proportional to dose at all sampling timepoints through Week 8 (Figure 6).

Figure 6. Median serum ustekinumab concentrations through Week 8 during induction phase in Study C0743T26
(Source: Figure 3 of C0743T26 CSR)



2.5.7 How do the PK concentration changes with time following chronic dosing in the maintenance phase?

Ustekinumab PK did not appear to change after chronic dosing in the maintenance phase.

Before administration of the first SC maintenance dose at Week 0 of CRD3003, the median serum ustekinumab concentrations for subjects in the placebo, 90 mg SC q12w, and 90 mg SC q8w treatment groups were 4.06, 3.43, and 3.82 µg/mL, respectively.

After the first maintenance dose at Week 0, steady-state appeared to have been reached at Week 12 or Week 8 prior to the administration of the second maintenance dose for the ustekinumab 90 mg SC q12w and 90 mg SC q8w, respectively (Figure 7). Thereafter, the median ustekinumab concentrations were maintained above detectable limits through Week 44 among subjects randomized to ustekinumab 90 mg SC q12w and 90 mg SC q8w. In contrast, the median ustekinumab concentrations were below detectable limits at Week 16 among subjects randomized to placebo maintenance.

In the ustekinumab 90 mg q8w group, the median serum ustekinumab trough concentrations at Weeks 8, 16, 24, 32, and 40 appeared consistent through Week 44 ranging from 1.97 to 2.24 µg/mL (Table 13). In the ustekinumab 90 mg q12w group, median serum ustekinumab trough concentrations at Week 12, 24, and 36 also appeared consistent from Week 12 through Week 44, with a range from 0.61 to 0.76 µg/mL.

Figure 7. Median serum ustekinumab trough concentrations through Week 44 during the maintenance phase in Study CRD3003
(Source: Figure 5 of CRD3003 CSR)

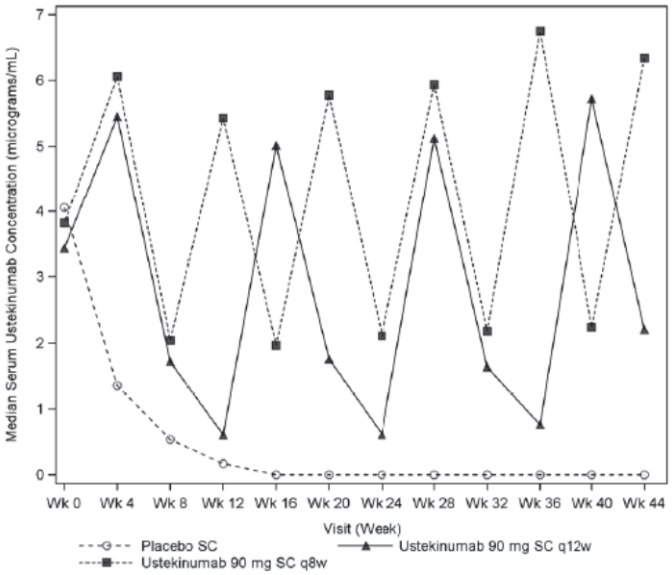


Table 13. Summary of serum ustekinumab trough concentrations through Week 44 during the maintenance phase in CRD3003
(Source: selected data from Table 3 of CRD3003 CSR)

		Ustekinumab SC maintenance	
		90 mg SC q12w (n = 132)	90 mg SC q8w (n = 131)
Week 0	N Mean (SD) Median (Range)	131 4.61 (4.16) 3.43 (0, 22.8)	125 5.35 (4.95) 3.82 (0, 24.6)
Week 8	N Mean (SD) Median (Range)	- 	124 2.83 (2.60) 2.05 (0, 15.9)
Week 12	N Mean (SD) Median (Range)	110 1.13 (1.70) 0.61 (0, 13.4)	-
Week 16	N Mean (SD) Median (Range)	- 	103 2.39 (2.00) 1.97 (0, 9.9)
Week 24	N Mean (SD) Median (Range)	95 0.86 (0.93) 0.62 (0, 6.6)	93 2.51 (2.06) 2.11 (0, 9.5)
Week 32	N Mean (SD) Median (Range)	- 	83 2.55 (1.95) 2.18 (0, 9.5)
Week 36	N Mean (SD) Median (Range)	81 0.93 (0.90) 0.76 (0, 5.3)	-
Week 40	N Mean (SD) Median (Range)	- 	81 2.62 (1.84) 2.24 (0, 9.9)

2.5.8 What is the proposed changes/addition in Section 12.7 Pharmacokinetics of the current labeling and is the proposal acceptable?

The Applicant proposed to add the PK information in the CD patients to Section 12.3 Pharmacokinetics of the current labeling. However, the proposal is not acceptable because the bioanalytical method (i.e., MSD-ECLIA) used to determine ustekinumab concentrations in the CD patients is not comparable to the original method (i.e., BV-ECLIA) used to generate the PK data in the psoriasis patients in BLA 125261.

Previously, comparability assessment of the BV-ECLIA and MSD-ECLIA assays has been reviewed by Dr. Jie Wang (see Clinical Pharmacology Review dated April 6, 2012 and December 18, 2012 under BLA 125261). The overall mean results of spiked and incurred samples from the MSD-ECLIA method were higher than those from the BV-ECLIA method by 22.36%, and the two methods were found not to be comparable (also see Section 2.9.1).

(b) (4)

Because the BV-ECLIA method is no longer in use, the Clinical Pharmacology Review team recommends that all PK information resulted from the BV-ECLIA method should be removed from the current labeling and substituted with PK information obtained from the MSD-ECLIA. The recommendation includes:

1. The removal of the C_{ss}, V_z/F, V_z, and CL value following IV administration in psoriasis patients
2. The inclusion of the C_{ss} data from psoriasis and CD patients
3. The inclusion of V_{ss} and CL values following IV administration in CD patients

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure in patients with CD?

Among several factors examined, body weight, serum albumin level, sex, race (Asian versus non-Asian), CRP level, TNFα antagonist failure status, and ADA were identified to have an effect on ustekinumab CL, whereas V2 (the central volume of distribution) was affected by body weight, sex, and serum albumin level.

Impact of these significant covariates on CL and V2 was small ranging from 2 to 19.5% which was not considered clinically meaningful.

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

No dosage regimen adjustment is recommended.

Age was a not significant covariate in the PopPK model, and no pediatric patients were evaluated in this BLA submission. Sex was a significant covariate for CL and V2 and race was a significant covariate for CL. The effect of sex and race was small (14% and 17%) and was not clinically significant. Hence, dose adjustment for sex and race is not necessary.

2.6.2.1 Body Weight

Body weight did not have a significant impact on clinical remission at Week 8 and Week 44; therefore, no dosing adjustment is needed for body weight. In addition to ustekinumab concentration, there were other significant cofounding factors affecting the clinical efficacy of ustekinumab in the induction phase.

The Clinical Pharmacology Reviewer performed subgroup analyses evaluating the ustekinumab concentrations in patients with the three body weight tiers (i.e., ≤55 kg, >55kg and ≤85 kg, and >85 kg) and compared the clinical remission rates across body weight groups to assess the impact of the body weight on clinical remission at Week 8 in the induction phase and clinical remission at Week 44 in the maintenance phase. These clinical remission rates were selected because they represented clinical endpoints that are meaningful to patients with CD.

For both the TNFα antagonist failure population (see Figure 8) and the TNFα antagonist non-failure population (see Figure 9), the median ustekinumab concentrations were higher for the ~6 mg/kg dose compared to 130 mg dose across all three body weight tiers, and the differences in median concentration were two-fold or greater. On the other hand, the remission rates across the body weight tiers were not consistently higher in the ~6 mg/kg group than in the 130 mg group. Take the TNFα antagonist failure population as an example, in spite of the > 2-fold higher median ustekinumab concentration in the ~6 mg/kg group compared to the 130 mg group across all three body weight tiers, the remission rate of the middle body weight tier (>55kg and ≤85 kg) was similar between the ~6 mg/kg group and 130 mg group (18.5% vs. 17.8%). Similarly, in the low body weight tier of the TNFα antagonist non-failure population, the median ustekinumab concentration was > 2-fold higher but the remission rate was lower in the ~6 mg/kg group compared to the 130 mg group (32.4% vs. 25.0%).

In summary, these data indicated that the differences in ustekinumab concentrations within the same body weight tier across two dose regimens and across body weight tiers within the same regimen did not translate into differences in the clinical remission rates. Nonetheless, when the combined data from all three body weight tiers are compared across two regimens, ~6 mg/kg dose showed a greater remission rate than the 130 mg dose (see Table 2)

Please also see the Pharmacometrics Review (addendum) from Dr. Jee Eun Lee for more information.

Figure 8. Median ustekinumab concentration at Week 8 (left panel) and clinical remission rate at Week 8 (right panel) for the three body weight groups in the induction phase; TNFα antagonist failure subjects (i.e., CRD3001) excluding those enrolled prior to study re-start

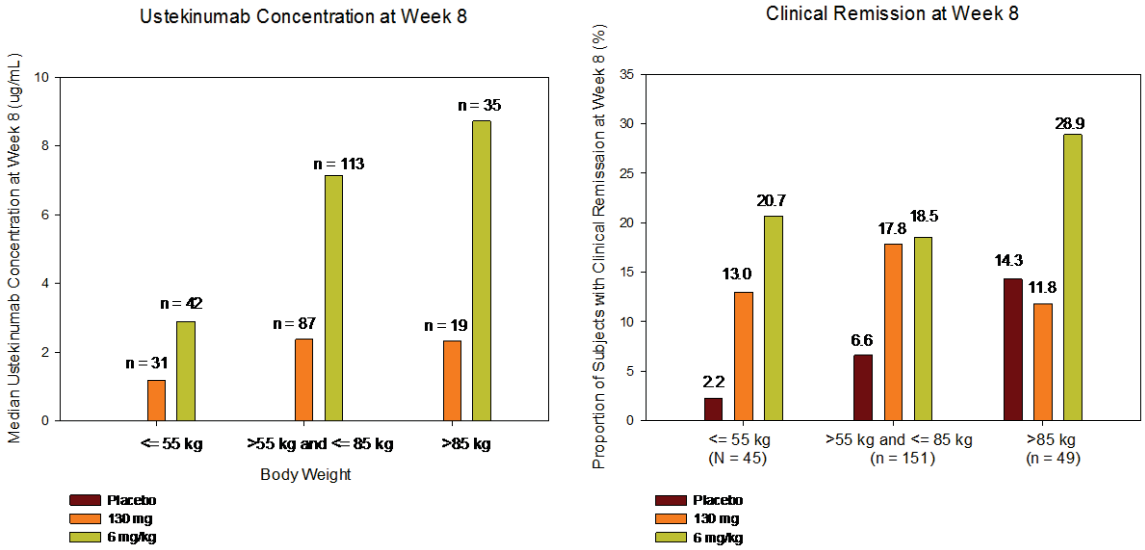
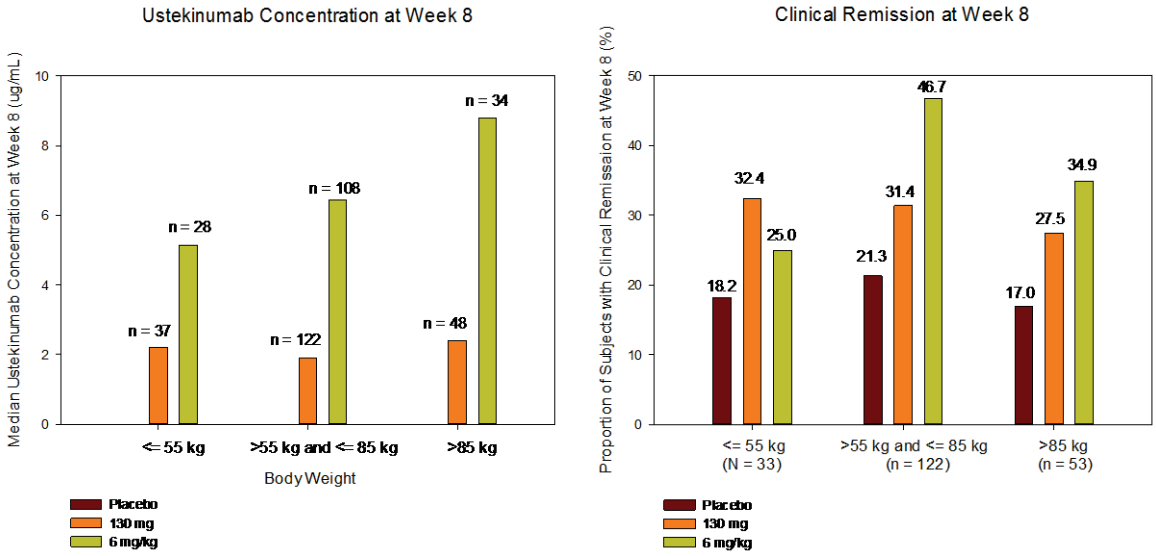


Figure 9. Median ustekinumab concentration at Week 8 (left panel) and clinical remission rate at Week 8 (right panel) for the three body weight groups in the induction phase; TNFα antagonist non-failure subjects (i.e., CRD3002) excluding those enrolled prior to study re-start



2.6.3 Does genetic variation impact exposure and/or response?

The Applicant has collected samples for DNA analysis in the CD patients, but no information has been submitted in the current BLA submission.

2.6.4 Immunogenicity

Two immunogenicity assays were used in the clinical development for CD, namely, the bridging enzyme immunoassay (EIA) method and the electrochemiluminescent immunoassay (ECLIA) method. The ECLIA method is an improvement over EIA method because it is drug-tolerant, i.e., capable of detecting the ADA in the presence of ustekinumb concentrations in patient who had ongoing ustekinumab treatment during the clinical trials. Only data collected using ECLIA method are discussed in this section. See Table 14 for a summary of the immunogenicity data submitted in the BLA.

Table 14. Summary of immunogenicity results in all the clinical studies

	NAP1002 (n = 140)	C0379T07 (n = 93)	C0743T26 (n = 427)	CRD3001, CRD3002, and CRD3003 (n = 1154)
ADA Incidence No. of Subjects (%)	 2/139 (1.4%)	 0/77 (0%)*	 3/427 (0.7%)	 27/1154 (2.3%)
ADA Titers	1:50, n = 2	-	1:10 to 1:80	≤ 1:800, n = 20 1:1600, n = 3 1:3200, n = 1 1:6400, n = 2 1:51200, n = 1
NAb No. of Subjects (%)	No results in the study report	-	 3/3 (100%)	 17/27 (63.0%)
Treatment Duration	One single IV dose	11 weeks in Population 1	16 weeks	52 weeks
Sampling Timepoints	Day 1, W8, 16	W0, 16, 28, 54	W0, 22, 36	W0, 6, 8, 20, 32, 44, 52
ADA Assay	ECLIA	EIA	EIA	ECLIA

*A total of 75.3% of the subjects in Population 1 (blinded to ustekinumab) were negative for antibodies to ustekinumab, and 24.7% of the subjects were classified as having undetectable antibodies to ustekinumab due to detectable ustekinumab levels in the samples
EIA, bridging enzyme immunoassay; ECLIA, electrochemiluminescent immunoassay

2.6.4.1 What is the incidence of the formation of ADA and the titers of ADA following administration of ustekinumab in CD patients?

Twenty-seven of 1154 (2.3%) treated subjects who received at least 1 dose of ustekinumab during induction or maintenance and had appropriate samples for antibodies were positive for ADA through Week 44 of CRD3003. Most of the ADA+ subjects (25 of 27) were positive by Week 24. A majority of these ADA+ subjects (20 of 27 subjects) had ADA titers at or below 1:800 (Table 14).

The incidence of ADA appeared similar between randomized subjects who received ustekinumab 90 mg SC q12w (3.0%, 4/132 subjects) and 90 mg SC q8w (2.3%, 3/131 subjects) maintenance therapy.

Reviewer's Comments

The immunogenicity samples from Studies C0379T07 and C0743T26 were analyzed by a (EIA) in which the detection of ADA was interfered by the presence of ustekinumab concentrations. Hence, the incidence of ADA positivity in these two studies was likely to be underestimated.

2.6.4.2 Do the antibodies to ustekinumab have neutralizing capability and what is the incidence (rate) of the formation of the neutralizing antibodies (NAb)?

Yes, antibodies to ustekinumab have neutralizing capability. As shown in Table 14, 17 of 27 (63.0%) ADA+ subjects in the phase 3 studies were NAb+.

2.6.4.3 Does the immunogenicity affect the PK of the therapeutic protein?

Yes, immunogenicity had a negative impact on the PK of ustekinumab.

In the heathy volunteer study NAP1002, two of 139 subjects became ADA+ following a single ustekinumab 6 mg/kg IV infusion. The mean half-life in these 2 subjects was shorter (11.7 and 17 days) than the mean half-life in the ADA- subjects (~25 days).

In the maintenance study CRD3003, the median serum ustekinumab concentrations over time were lower in ADA+ subjects compared to those in ADA- subjects; the difference was two- to three-fold in the 90 mg SC q12 w group and at least three-fold in the 90 mg SC q8w group (Figure 10).

In response to the FDA's Information Request (IR) dated May 10, 2016, the Applicant further provided the individual concentration-time profile for each of the 27 ADA+ subjects in Study CRD3003 for assessing the impact of immunogenicity on PK. The median ustekinumab concentration–time profile for ADA- subjects who received similar ustekinumab dose regimen was included in each subject concentration-time profile for comparison (SDN 22; June 14, 2016). These data at the individual subject level were used for additional analysis as described below.

To determine the impact of immunogenicity on PK at the subject level, the Clinical Pharmacology reviewer evaluated the observed data through: (1) the comparison of the individual concentration-time profile of ADA+ subjects with the median concentration-time profile for the ADA- subjects who received the same ustekinumab dose, and (2) the comparison of the steady state trough concentration data between ADA+ samples and ADA- samples within each ADA+ subject. A negative impact was concluded when ustekinumab concentrations for ADA+ samples were lower than the concentrations for ADA- samples in a given individual and/or the overall concentration-time curve in a given individual deviated from (or lower than) the median concentration-time profile for the ADA- subjects who received similar ustekinumab dose regimen.

Table 15 summarizes the assessment results of the impact of immunogenicity on PK based on the reviewer's evaluation of the individual concentration-time profile. Among the 27 ADA+ subjects, the impact of immunogenicity on PK could not be assessed in 9 (33.3%) subjects and no impact was found in 5 (18.5%) subjects.

A negative impact of ADA on PK was observed in the remaining 13 (48.1%) subjects; the majority (9/13 or 69.2%) of these subjects was NAb+. The mean ustekinumab concentration for ADA+ samples was reduced by 42.8% to 89.1% compared to the mean concentration for ADA- samples in seven subjects. This extent of concentration decrease in ADA+ subjects was larger than the 13% higher CL as predicted by the PopPK model (see Section 2.6.1).

Figure 10. Median serum ustekinumab concentrations over time by ADA status during the maintenance study CRD3003 in treated subjects who were randomized to placebo (top panel), usekinumab SC 90mg q12w (middle panel), and usekinumab SC 90mg q8w (bottom panel)
(Source: Figure 6 CRD3003 CSR)

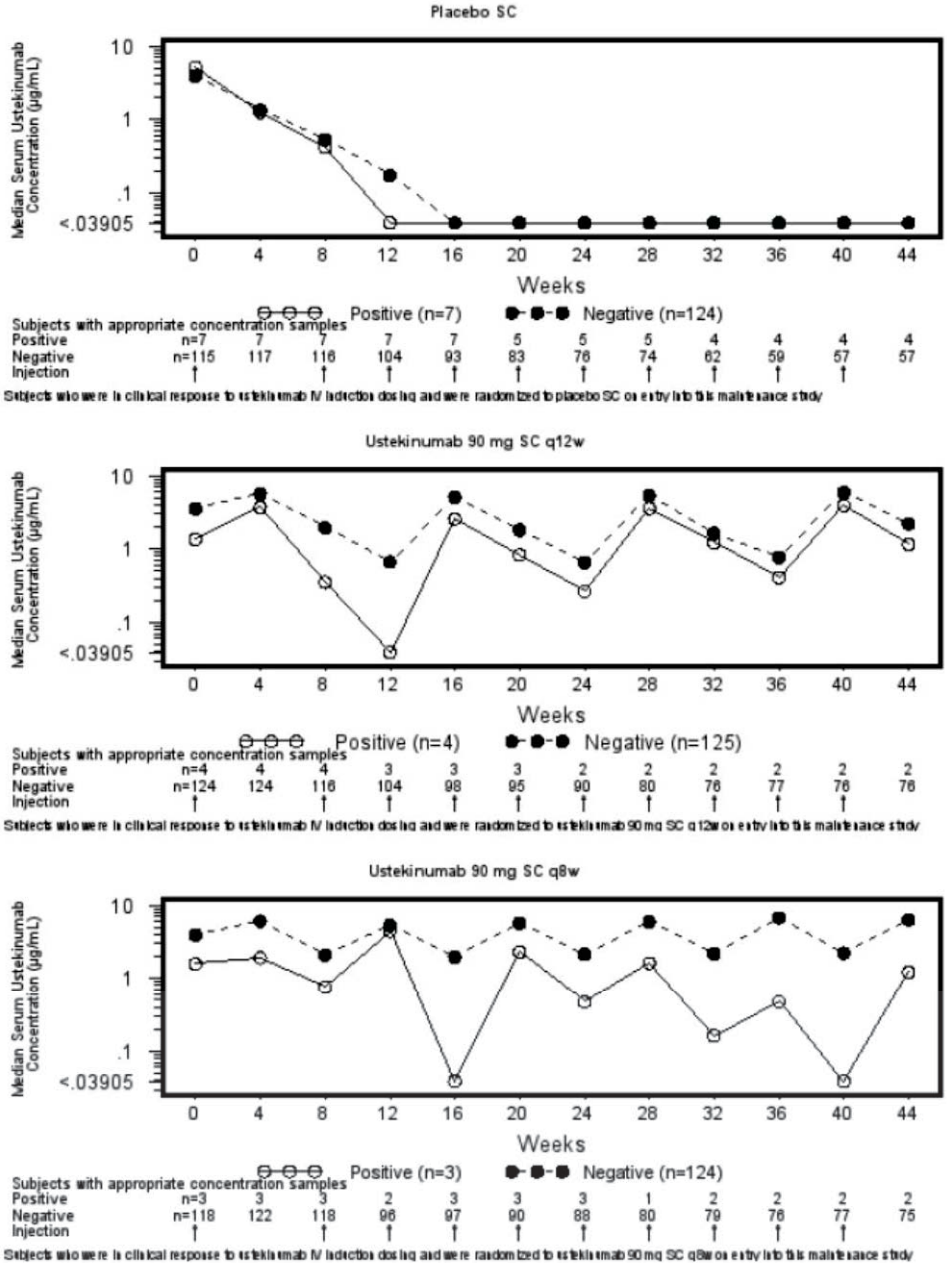


Table 15. Summary of serum ustekinumab concentration data before and after the ADA seroconversion

	Negative impact	No Impact	Impact cannot be determined[#]
ADA+	13/27 (48.1%)	5/27 (18.5%)	9/27 (33.3%)
NAb+	9/13 (69.2%)	3/5 (60%)	5/9 (55.5%)
Subject ID	10086, 10118, 10193, 10539, 10628, 10796, 10929, 10964, 11078, 20234, 20268, 20303, 20809	10660, 10682, 20395, 20503, 21021	10094, 10162, 10351, 10766, 20114, 20238, 20803, 20848, 20879
Mean Concentration Reduction[*]	42.8% (10086) 74.7% (10193) 80.3% (10539) 68.2% (10628) 63.8% (20234) 50.5% (20268) 89.1% (20809)		

*The magnitude of impact of ADA on PK can be quantified with certainty in seven subjects. The remaining subjects had samples below the limit of quantitation at the reference timepoint when ADA was negative, and the reduction in concentration value cannot be determined. For trough samples with undetectable concentration, concentration value was assigned as ½ of the lower limit of quantitation (i.e., 0.084 µg/mL).

[#]The reasons includes undetectable trough concentration at the reference timepoint when ADA was negative, insufficient samples for overall assessment, ADA+ at Week 0 of the maintenance study, and undetectable concentrations for all trough concentration samples.

2.6.4.4 What is the impact of immunogenicity on clinical efficacy?

The assessment of the impact of immunogenicity on clinical efficacy is inconclusive because the number of subjects who became ADA+ was small in the phase 3 studies.

Following ustekinumab treatment, 1 subject (0.2%) each was identified to be ADA positive in CRD3001 and CRD3002. These two ADA+ subjects were not in clinical response at Week 6 and not enrolled in maintenance study (i.e., CRD3003). Because of the small number of ADA+ subjects, it was not feasible to perform analyses for efficacy versus antibody status in these induction two studies.

Among 396 subjects who were randomized in the maintenance study and who had appropriate samples for immunogenicity assessment, 14 (3.5%) were ADA+ at one point during utstekinumab treatment. The proportion of ADA+ subjects between Week 44 remitters and Week 44 non-remitters appeared similar in both the ustekinumab 90 mg SC q12 w and 90 mg SC q8w groups (Table 16)

Table 16. The proportion of ADA positivity in randomized subjects who achieved clinical remission at Week 44 and in subjects who did not achieve clinical remission in CRD3003
(Source: calculated from TEFCREM11 of CRD3003 CSR)

	Immunogenicity status (ADA+/ ADA-) by treatment group and remission status, [Number of subjects (%)]				
Treatment group	Placebo SC	90 mg SC q12w	90 mg SC q8w	Combined	Total
N	131	129	127	256	387
Subjects achieved clinical remission at Week 44					
N	47	63	68	131	178
ADA positive	1 (2.1%)	2 (3.2%)	2 (2.9%)	4 (3.1%)	5 (2.8%)
ADA negative	46 (97.9%)	61 (96.8%)	66 (97.1%)	127 (96.9%)	173 (97.2%)
Subjects did not achieve clinical mission at Week 44					
N	84	66	60	125	209
ADA positive	6 (7.1%)	2 (3.0%)	1 (1.7%)	3 (2.4%)	9 (4.3%)
ADA negative	78 (92.9%)	64 (97.0%)	59 (98.3%)	122 (97.6%)	200 (95.7%)

2.6.4.5 What is the impact of immunogenicity on clinical safety?

The development of antibodies to ustekinumab did not appear to be associated with injection-site reactions in randomized subjects in CRD3003. However, the results should be interpreted with caution because of the infrequent ADA assessment schedule in the study.

Among 396 subjects who were randomized in the maintenance study and who had appropriate samples for immunogenicity assessment, 14 (3.5%) were ADA+ from Week 0 of an induction study through Week 44 of maintenance. None of the 14 treated subjects who were ADA+ had an injection-site reaction.

The remaining 382 treated subjects were ADA-. Six (1.6%) of these subjects experienced a placebo injection-site reaction. Twelve (4.7%) subjects experienced an ustekinumab injection-site reaction; three (2.3%) of these subjects was in the ustekinumab 90 mg SC q12w group and nine (7.0%) were in the ustekinumab 90 mg SC q8w group.

2.6.4.6 What is the impact of immunomodulators on immunogenicity?

The use of concomitant immunomodulators including 6-MP, AZA, and MTX had an impact on immunogenicity. The proportion of ADA+ subject was higher among those who received immunomodulators (7/375 subjects, 1.9%) compared with those who did not receive immunomodulators (20/779 subjects, 2.6%).

2.7 Extrinsic Factors

2.7.1 What is the impact of extrinsic factors on ustekinumab PK?

The use of concomitant immunomodulators (i.e., 6-MP, AZA, or MTX) and smoking status at baseline (i.e., at Week 0 of an induction study) were evaluated as extrinsic factors in the PopPK analysis. Both of these factors were found not to be a significant covariate, and hence, had no impact on ustekinumab PK. See Section 2.5.2 for more information.

The median observed ustekinumab concentrations appeared similar with or without concomitant immunomodulators during the induction phase (Figure 11) and the maintenance phases (Figure 12)

Figure 11. Median serum ustekinumab concentration through Week 8 by baseline immunomodulator (6MP/AZA/MTX) status in Study CRD3001 (upper panels) and Study CRD3002 (lower panels) excluding those enrolled prior to study restart
(Source: Appendix B.5 and B.2 of Module 2.7.2 Summary of Clinical Pharmacology Studies)

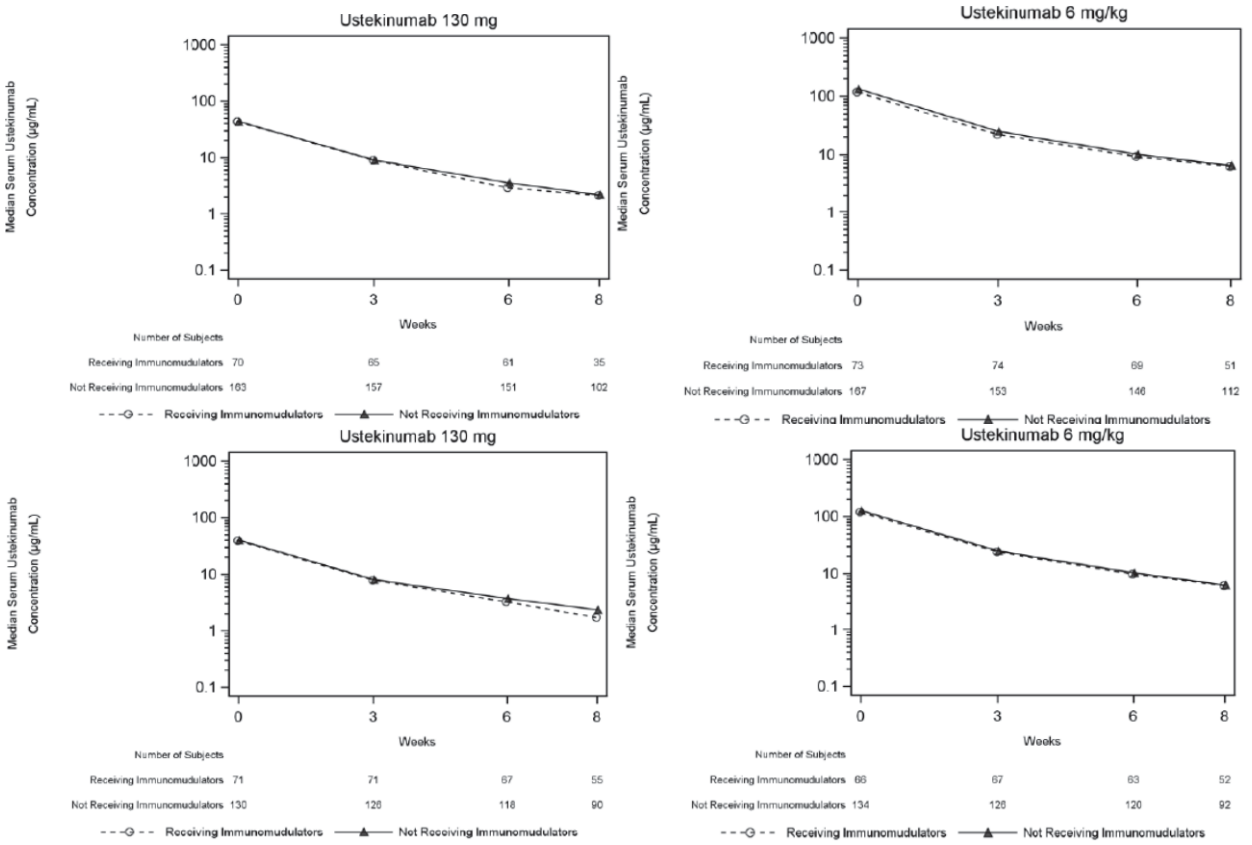
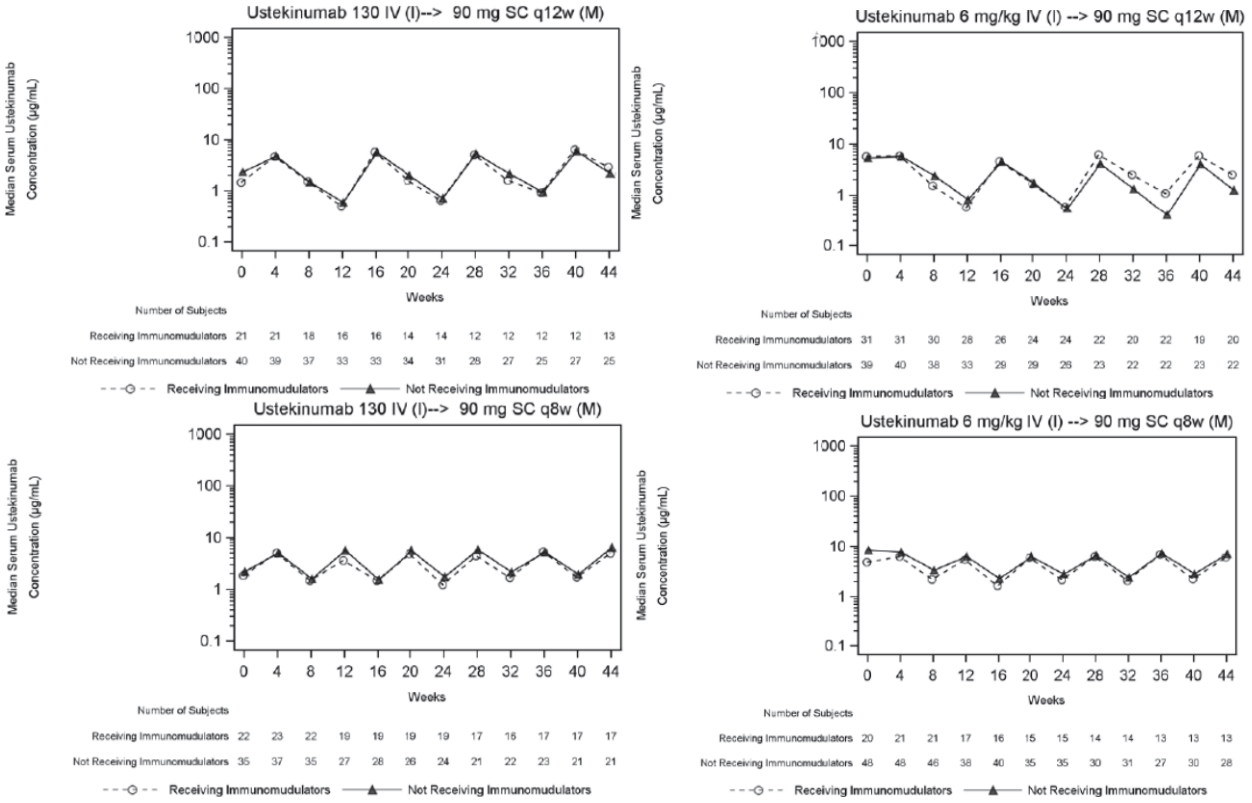


Figure 12. Median serum ustekinumab concentration through Week 44 by baseline immunomodulator (6MP/AZA/MTX) status in subjects who were randomized to 90 mg SC q12w (upper panels) and 90 mg SC q8w (lower panels) in CRD3003
(Source: Appendix B.4 and B.5 of Module 2.7.2 Summary of Clinical Pharmacology Studies)



2.7.2 What is the impact of extrinsic factors on efficacy?

The combined use of concomitant oral corticosteroids and 6MP/AZA/MTX at baseline appeared to decrease efficacy of ustekinumab. However, the use of corticosteroids or immunomodulators alone at baseline was not associated with reduced efficacy. Because of the subgroup analysis and the small number of subjects receiving the corticosteroid-immunomodulator combination at baseline, the results should be interpreted with caution.

When oral corticosteroids and 6-MP/AZA/MTX were used together, the odd ratios (OR) and 95% confidence intervals (CI) for the proportion of subjects in clinical remission at Week 44 were lower for the ustekinumab 90 mg SC q12w (Figure 13) and 90 mg SC q8w (Figure 14) 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). This effect was not observed in subjects receiving concomitant oral corticosteroids or 6MP/AZA/MTX alone at baseline, however.

Figure 13. Odds ratio and 95% confidence intervals for comparing the proportion of subjects in clinical remission at Week 44 in the ustekinumab 90 mg SC q12w group versus the placebo group by concomitant CD medications at baseline of the induction study
(Source: GEFCREM07 of CRD3003 CSR)

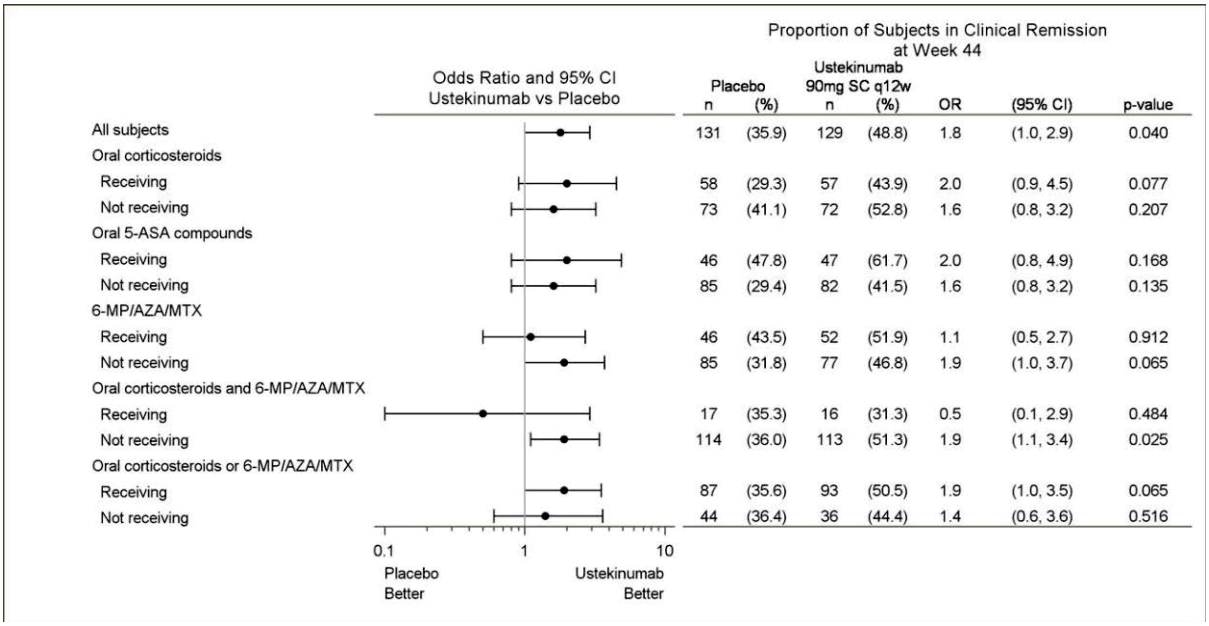
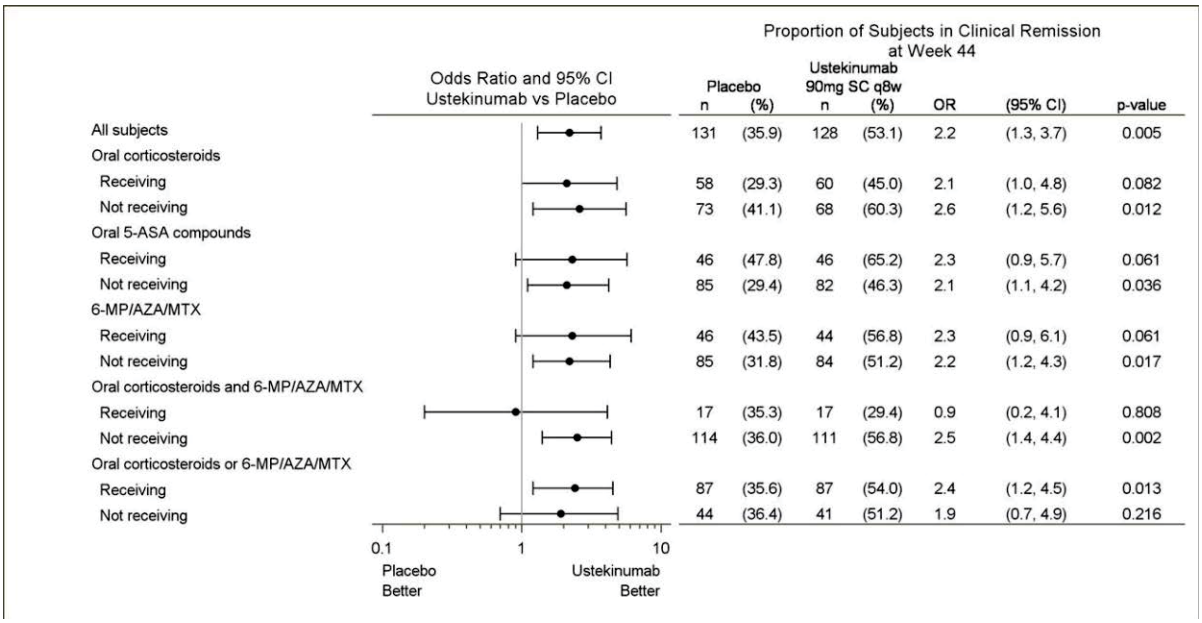


Figure 14. Odds ratio and 95% confidence intervals for comparing the proportion of subjects in clinical remission at Week 44 in the ustekinumab 90 mg SC q8w group versus the placebo group by concomitant CD medications at baseline of the induction study
(source: GEFCREM08 of CRD3003 CSR)



2.7.3 What is the impact of extrinsic factors on safety?

The use of concomitant immunomodulators (i.e., 6MP/AZA/MTX) at baseline was associated with a higher incidence of serious infections (4.5% vs. 2.2%, Table 17), whereas the use of concomitant corticosteroids at baseline was associated with a lower incidence of serious infection (1.5% vs. 4%, Table 18). The observed steroid effect is counterintuitive because augmented immunosuppressive effect would be expected when ustekinmuab was combined with corticosteroids. The results should be interpreted with caution given the low number of events.

Table 17. Number of treatment-emergent adverse events, serious adverse events, infections, serious infections or adverse events leading to discontinuation of study agent on maintenance therapy (up to 44 weeks) per hundred subject-years of follow-up by induction baseline immunomodulator usage; treated subjects randomized as responders to ustekinumab in C0743T26 and cRD3003
(Source: TUSSFSUB02A of Response to Information Request Received 25 July 2016; SDN 29)

	Receiving IMM[b] at Baseline		Not Receiving IMM[b] at Baseline	
	Placebo[c]	Ustekinumab[c] [d]	Placebo[c]	Ustekinumab[cd]
Subjects treated	70	112	136	223
Avg duration of follow-up (weeks)	27.17	33.40	24.65	30.25
Avg duration of treatment (weeks)	21.13	25.55	18.94	22.33
Subjects who discontinued study agent because of adverse events	2 (2.9%)	5 (4.5%)	11 (8.1%)	10 (4.5%)
Subjects with 1 or more				
Adverse events	54 (77.1%)	81 (72.3%)	111 (81.6%)	178 (79.8%)
Serious adverse events	8 (11.4%)	11 (9.8%)	16 (11.8%)	22 (9.9%)
Infections[e]	28 (40.0%)	46 (41.1%)	57 (41.9%)	95 (42.6%)
Serious infections[e]	3 (4.3%)	5 (4.5%)	0	5 (2.2%)
Total subject-years of follow-up	37	72	64	130
Event rate per 100 subject-years (number of events)				
Adverse events	585.02 (214)	443.48 (319)	650.00 (419)	565.80 (734)
Serious adverse events	24.60 (9)	19.46 (14)	24.82 (16)	20.04 (26)
Infections[e]	123.02 (45)	127.90 (92)	125.66 (81)	127.19 (165)
Serious infections[e]	8.20 (3)	6.95 (5)	0.00 (0)	4.63 (6)
Adverse events leading to discontinuation of study agent	5.47 (2)	9.73 (7)	18.62 (12)	7.71 (10)

[a] C0743T26 from Week 8 to Week 22; CNTO1275CRD3003 from Week 0 to Week 44.
[b] Immunomodulators (AZA, 6-MP, or MTX).
[c] Includes data up to the time of meeting loss of response criteria for dose adjustment.
[d] ustekinumab q8w and q12w combined.
[e] Infection as assessed by the investigator.

Table 18. Number of treatment-emergent adverse events, serious adverse events, infections, serious infections or adverse events leading to discontinuation of study agent on maintenance therapy (up to 44 weeks) per hundred subject-years of follow-up by induction baseline corticosteroid usage; treated subjects randomized as responders to ustekinumab in C0743T26 and CRD3003
(Source: TUSSFSUB02B of Response to Information Request Received 25 July 2016; SDN 29)

	Receiving corticosteroid[b] at Baseline		Not Receiving corticosteroid[b] atBaseline	
	Placebo[c]	Ustekinumab[c] [d]	Placebo[c]	Ustekinumab[cd]
Subjects treated	78	133	128	202
Avg duration of follow-up (weeks)	23.48	28.43	26.74	33.19
Avg duration of treatment (weeks)	17.05	20.49	21.30	25.32
Subjects who discontinued study agent because of adverse events	7 (9.0%)	6 (4.5%)	6 (4.7%)	9 (4.5%)
Subjects with 1 or more				
Adverse events	68 (87.2%)	109 (82.0%)	97 (75.8%)	150 (74.3%)
Serious adverse events	12 (15.4%)	14 (10.5%)	12 (9.4%)	19 (9.4%)
Infections[e]	38 (48.7%)	57 (42.9%)	47 (36.7%)	84 (41.6%)
Serious infections[e]	1 (1.3%)	2 (1.5%)	2 (1.6%)	8 (4.0%)
Total subject-years of follow-up	35	73	66	129
Event rate per 100 subject-years (number of events)				
Adverse events	721.30 (254)	618.81 (450)	575.75 (379)	467.66 (603)
Serious adverse events	34.08 (12)	22.00 (16)	19.75 (13)	18.61 (24)
Infections[e]	139.15 (49)	130.64 (95)	116.97 (77)	125.64 (162)
Serious infections[e]	2.84 (1)	2.75 (2)	3.04 (2)	6.98 (9)
Adverse events leading to discontinuation of study agent	22.72 (8)	11.00 (8)	9.11 (6)	6.98 (9)

[a] C0743T26 from Week 8 to Week 22; CNTO1275CRD3003 from Week 0 to Week 44.
[b] Includes budesonide.
[c] Includes data up to the time of meeting loss of response criteria for dose adjustment.
[d] ustekinumab q8w and q12w combined.
[e] Infection as assessed by the investigator

2.7.4 What are the drug-drug interactions?

No formal drug-drug interaction studies were conducted for ustekinumab in CD.

Concomitant 6-MP, AZA, or MTX use in CD patients was found to have no impact on ustekinumab PK (see Section 2.7.1).

2.7.5 What other co-medications are likely to be administered to the target population?

Corticosteroids and the immunomodulators 6MP, AZA and MTX are the most common co-medications that are administered to patients with CD.

2.7.6 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions? Is there a need for assessing drug-disease interaction in PMC study?

Corticosteroids, 6MP, AZA, and MTX are immunosuppressants that could potentially enhance the immunesuppressive effects of ustekinumab in CD patients. See Section 2.7.3 for more information regarding the use of concomitant immunomodulators and corticosteroids.

In addition, patients with CD have elevated levels of proinflammatory cytokines which can suppress the expression of some cytochrome P450 (CYP) enzymes. The suppression of the CYP enzymes could be normalized upon the disease improvement following treatment with ustekinumabe. As a result, the exposure of CYP substrates could be reduced when the CD is improved and the proinflammatory cytokines are normalized. One potential impact of the drug-drug interaction is the loss of efficacy of the concomitant small molecule CYP substrate drugs which CD patients take. Because of this potential drug-drug interaction, the Clinical Pharmacology review team recommends a PMC study to evaluate the impact of ustekinumab treatment on the exposure of CYP substrates in CD patients.

2.8 General Biopharmaceutics

2.8.1 What formulation was introduced during the development program? (Include a table listing all the products used throughout the clinical development programs.) What formulation strength is available for the to-be-marketed drug product?

For the CD indication, there are two commercial products: 5 mg/mL LIV for IV dosing and 90 mg/mL prefilled syringe for SC dosing. No manufacturing changes have been made to the 90 mg/mL formulation which is approved for SC dosing under BLA 125261. The to-be-marketed 5 mg/mL LIV formulation was newly developed for the IV administration in the clinical program for CD.

In the Phase 3 studies of ustekinumab in CD, the Applicant originally designed to include a 5 mg/mL diluted formulation with 130 mg/26 mL per vial for induction dosing that was intended to be marketed. However, a stability issue was identified with the batch of IV drug used in the study after 40 subjects had been randomized. Subsequently, the Applicant substituted the dilute LIV formulation (5 mg/mL) with the approved 90 mg/mL LIV ustekinumab formulation for the protocol-specified IV induction administrations. Table 19 summarizes the IV and SC ustekinumab formulations that were used in the CD trials.

The final IV presentation for commercial use will be a new dilute formulation for IV administration comprising 130 mg ustekinumab in 26 mL (5 mg/mL) in each vial. The 5 mg/mL LIV has the same excipient components as 90 mg/mL LIV, with the addition of ethylene-diaminetetraacetic acid (EDTA; 0.02 mg/mL) and L-methionine (0.4 mg/mL). The dilute 5 mg/mL LIV formulation was shown to have biophysical and biochemical properties comparable with those of the 90 mg/mL LIV formulation. See CMC review from Dr. Zhenzhen Liu for more information.

The Applicant conducted a PK comparability NAP1002 study at a single dose (6 mg/kg) in healthy subjects to assess the PK of the new dilute 5 mg/mL LIV formulation with the previously approved 90 mg/mL LIV formulation. The new dilute 5 mg/mL LIV formulation is proposed to be the commercial product for the IV induction.

Table 19: Ustekinumab formulations used in the CD studies
(Source: Table 1 of Module 2.5 Clinical Overview)

	Phase 1	Phase 2		Phase 3		
Route/Formulation	CNTO1275 NAP1002	C0379T07[a]	C0743T26	CNTO1275 CRD3001	CNTO1275 CRD3002	CNTO1275 CRD3003
(b) (4)		IV, SC				
	IV		IV	IV	IV	IV
			SC			SC
				IV	IV	
To-be-marketed 5 mg/mL (vial)	IV					
IV=intravenous; SC=subcutaneous.						
(b) (4)						

2.8.2 Was the proposed to-be-marketed formulation comparable to the formulation used in the pivotal clinical trials with respect to PK and/or pharmacodynamics?

Yes, the proposed to-be-marketed 5 mg/mL LIV formulation was comparable to the 90 mg/mL LIV formulation that was used in the Phase 3 studies.

The geometric mean ratio of C_{max} between the two formulations was 0.967, with a 90% CI of 0.932 to 1.003. The geometric mean ratios for AUC_{inf} and AUC_{last} were the 0.971 (0.914 – 1.031) and 0.971 (0.920 – 1.024), respectively. This systemic exposure of ustekinumab was similar between the two formulations based on the standard bioequivalence interval of 0.80 to 1.25.

2.9 Analytical Section

2.9.1 What bioanalytical methods are used to assess the therapeutic protein concentrations?

Two bioanalytical methods (ELISA and MSD-ECLIA) were utilized to determine the ustekinumab concentrations collected in clinical studies in the clinical development program for CD. A third method (BV-ECLIA), not used in studies in this BLA, was used in the psoriasis clinical development program and the data are included in section 12.3 of the current product labeling. Table 20 outlines the bioanalytical methods that were used in analyzing ustekinumab concentrations in the psoriasis and CD programs.

For the MSD-ECLIA method that was used to analyze clinical samples in the CD program, CP2008V-054 -A10 to -A12 are new to BLA 761044 and were not submitted to BLA 125261. CP2008V-054-A10 presents the partial validation for the robotic-assisted sample dilution for ustekinumab PK with only 1:10 dilution script on the Tecan Freedom EVO® 200. CP2008V-054-A11 describes a successful method transfer between the Tecan Freedom EVO® 200 and Hamilton liquid handling systems. Finally, CP2008V-054-A12 presents a successful cross-validation for the transfer of the ECLIA method from the (b) (4) to the (b) (4) laboratories.

Table 20. Bioanalytical methods that were used in analyzing ustekinumab concentrations

	ELISA	BV-ECLIA	MSD-ECLIA
Labeling information	-	Psoriasis data in current labeling	New data from CD patients data to be added to current labeling
Status of the assay	No longer in use	No longer in use	Currently in use
LLOQ (10x dilution, what value to report)	0.00844 µg/mL	0.01688 µg/mL	0.01688 µg/mL
BLA 761044 in CD			
Clinical studies	C0379T07	-	C0743T26, CRD3001, CRD3002, CRD3003, and NAP1002
Validation reports	CP2001V-009, CP2001V-009-A1	-	CP2008V-054 and CP2008V-054-A1 to -A7 and -A9 to -A12
BLA 125261 in Psoriasis			
Phase 3 clinical studies	-	C0743T08/09	C0743T08/09
Time period	-	Prior to long-term extension	Long-term extension
Mean concentration relative to BV-ECLIA method (clinical samples)	-	100%	Higher by: 74.2% to 106% (45 mg) 68.8% to 114% (90 mg)
Mean concentration relative to BV-ECLIA method (QC and incurred samples)	Higher by 30.2%	100%	Higher by 22.4%
Validation reports	CP2001V-009	CP2007V-001-A1 and CP7007V-001-A2	CP2008V-054 and CP2008V-054-A5 to -A9

ELISA, enzyme-linked immunosorbent assay; BV-ECLIA, electrochemiluminescent immunoassay method on BioVeris platform; MSD-ECLIA, electrochemiluminescent immunoassay method on Meso Scale Discovery platform; LLOQ, lower limit of quantification; CD, Crohn's disease; QC, quality control

During the review of the serum ustekinumab concentration data, the Clinical Pharmacology reviewer noted two numeric values of lower limit of quantitation (LLOQ) in the PK concentration dataset (adpc.xpt) for the Phase 2b and Phase 3 studies, whereas the Applicant stated that only the MSD-ECLIA method was used for analyzing PK samples in all CD trials (see IR dated May 10, 2016).

The Applicant confirmed that only the MSD-ECLIA assay platform was used for the determination of ustekinumab concentrations in the Phase 2b and Phase 3 studies (SDN 14; May 13, 2016). There are two different values under the "PCLLOQ" column in the PK concentration datasets because of the different dilution factors used in sample analysis. Specifically, a 1:10 sample dilution was used for PK samples in the low concentration range, whereas a 1:500 sample dilution was used for PK samples in the high concentration range.

Reviewer's Comments

The Applicant's clarification of the two different values under the "PCLLOQ" column in the PK concentration dataset is acceptable.

2.9.2 Briefly describe the methods that are used to assess the serum protein biomarkers and mRNA expression?

For the serum samples collected in Study C0743T26, the levels of IL-23, IL-17A, and IL-17 were analyzed using the immunoassay kits (catalog # 03-0112-XX, 03-0103-00, and 03-0102-00, respectively) from Singulex. For the serum samples collceted in Studies CRD3001, CRD3002, and CRD3003, serum levels of the 17 selected analytes were analyzed by different commercial immunoassay kits as summarized in Table 21.

Table 21. Immunoassay kits used for the analysis of serum protein biomarkers in Studies CRD3001, CRD3002, and CRD3003
(Source: Table 3 of Biomarker Technical Report EDMS-ERI-113107871)

Analytes	LLOQ (pg/mL)	1/2 of LLOQ (pg/mL)	Assay Manufacturer	Catalog #
IFNγ	0.24	0.12	MesoScale Discovery	K15049G
IL-6	0.15	0.08	MesoScale Discovery	K15049G
IL-8	0.13	0.07	MesoScale Discovery	K15049G
TNFα	0.06	0.03	MesoScale Discovery	K15049G
GM-CSF	0.23	0.12	MesoScale Discovery	K15050G
IL12p40	0.75	0.38	MesoScale Discovery	K15050G
CK-MB	0.176 ng/mL	0.088 ng/mL	MesoScale Discovery	N45CA-1
CRP	13.90 pg/mL	6.95 pg/mL	MesoScale Discovery	K15198G
SAA	17.10 pg/mL	8.55 pg/mL	MesoScale Discovery	K15198G
Haptoglobin	3.13 ng/mL	1.56 ng/mL	ALPCO Diagnostics	41-HAPHU-E01
IL-23	0.1 pg/mL	0.05 pg/mL	Singulex	03-0112-XX
MMP-1	0.20 ng/mL	0.10 ng/mL	MesoScale Discovery	K15034C
MMP-3	0.20 ng/mL	0.10 ng/mL	MesoScale Discovery	K15034C
MMP-9	0.98 ng/mL	0.49 ng/mL	MesoScale Discovery	K15034C
MPO	90.77	45.39	Millipore	HNDG3MAG-36K-01
IL-17A	0.017	0.0085	Singulex	03-0103-00
IL-17F	0.39	0.195	Singulex	03-0102-00
Sample results <LLOQ were reported as 1/2 of the LLOQ.				

For the tissue biopsy samples obtained in Study C0743T26, total RNA was isolated using miRNAeasy kit following the manufacturer's instructions (Qiagen Inc., Valencia, CA). The mRNA expression was analyzed by Affymetrix GeneChip HT HGU133 + PM 96-Array plates (Affymetrix, Santa Clara, CA) and Array Studio software version 8.0 (OmicSoft Corp., St. Morrisville, NC). See Genomics Group Review from Dr. Anuradha Ramamoorthy for more information (Appendix A).

2.9.3 What assays were used to assess the immunogenicity samples from the CD clinical trials?

See Table 14 for the immunogenicity assays that were used to assess ADA to ustekinumab in the CD clinical trials. The ECLIA assay is drug-tolerant and is able to detect antibodies to

ustekinumab in the presence of expected serum concentrations of ustekinumab. The detection of ADA was interfered by the presence of ustekinumab concentrations in the EIA assay method. Refer to the Quality Review from BLA 125261 for more information.

2.10 Biomarker and Tissue Transcriptomics Analysis

The Applicant assessed a series of serum proteins in C0743T26 and in the combined CRD3001, CRD3002, and CRD3003 studies to assess the effects of ustekinumab on biomarkers related to CD and the mechanism of action of ustekinumab. The Applicant also explored the pharmacodynamic (PD) effect of ustekinumab on the expression of mRNA in the Phase 2b study C0743T26. The protein analytes/mucosal biopsy samples, assessment timepoints, the number of subjects evaluated, and the rationale for the selection of the subject samples are summarized in Table 22.

Table 22. Summary of serum biomarker and gene expression analyses

Study	Protein Analytes/Mucosal Biopsy Samples	Timepoints	Analysis Performed	Serum or Biopsy Sample Selection
C0743T26	IL-17A, IL-17F, IL-23	BL, W4, 6, and 22	Pilot: 88 subjects at BL and W22 Expanded cohort: 299 samples at BL, 298 samples at W4	R: CDAI drop ≥ 100 from baseline; NR: CDAI drop < 100 from baseline
CRD3001, CRD3002, and CRD3003	Matrix metalloproteinases: MMP-1, MMP-3, MMP-9 Cytokines: IFNγ, TNF, IL-6, IL-8, IL-12p40, IL-23, IL-17A, IL-17F, GM-CSF Acute Phase Reactants: CRP, SAA, haptoglobin Inflammatory markers: myeloperoxidase, CK-MB	BL W3 and W6 during induction in CRD3001 and CRD3002 W8 and W44 during maintenance in CRD3003	Primary (disease vs. healthy, post- vs. pre-treatment): 200 subjects in CRD3001 219 subjects in CRD3002	First selection: CRD3001 and CRD3002 subjects who also participated in the endoscopy substudy and provided biopsy samples Second selection: by % change in CDAI at W8; highest % change for R, minimal % change for NR
C0743T26	Inflamed and non-inflamed regions of colon and ileum	BL, Weeks 6 and 22	88 subjects with 574 biopsy samples	See Appendix A

IL, interleukin; MMP-1, matrix metalloproteinases; IFNγ, interferon gamma; TNF, tumor necrosis factor; GM-CSF, granulocyte macrophage colony-stimulating factor; CRP, C-reactive protein; SAA, serum amyloid A; CK, creatine kinase; W, week; BL, baseline; R, responder; NR, non-responder

2.10.1 What conclusion(s), if any, can be made from the analyses of protein analytes before and after ustekinumab treatment in CD patients?

Due to the limitations of the biomarker analyses, definitive conclusion cannot be drawn regarding the impact of ustekinumab on CD disease-related and mechanism-of-action-related markers on induction and maintenance therapy.

The Applicant evaluated three serum protein anlaytes (IL-17A, IL-17F, IL-23, see Table 22 for additional details) in Study C0743T26. Based on the analysis results, the Applicant concluded that IL-17A levels are related to the degree of inflammation in CD and IL-17A could be a potential biomarker of response to ustekinumab.

The Applicant also conducted the protein analysis for 17 analytes in a subset of subjects from the phase 3 studies. They concluded that results demonstrated a specific biological effect of ustekinumab in mediating efficacy in responders as compared to placebo responders, including the efficacy in induction and maintenance phase.

In reviewing the data, the Clinical Pharmacology Reviewer identified several limitations in the analyses, making it difficult to draw definitive conclusion from the study results. Limitations of the protein analyses include:

- All the serum analyses were exploratory with protein levels determined in subsets of patients in both the phase 2 and phase 3 studies.
- The comparison of the protein levels between CD patients in phase 3 studies and healthy subjects was based on a small sample of healthy individuals. No information has been provided for the samples from the healthy subjects including the source of the samples and the demographics of the healthy subjects.
- For the comparison of protein levels between responders and non-responders in the phase 3 studies, subjects with the greatest and minimal response, as measured by the % change in CDAI score were chosen. This comparison of selected subjects at the two extremes likely overestimated the differences in the protein levels between responders and non-responders.
- A high variability in protein levels was observed in the data, and there were no adjustments for multiple statistical comparisons. A >1.5 fold change in protein levels was defined as the criterion for statistical significance between group comparisons; however, the clinical meaningfulness of this degree of changes is not known.

2.10.2 What pharmacodynamics changes in mRNA expression were resulted from ustekinumab treatment in patients with CD?

One of the secondary objectives of Study C0743T26 was to explore the pharmacodynamics of ustekinumab therapy, including effect of treatment on tissue mRNA expression. Analyses were performed to identify: (1) disease profile (colonic or ileal genes modulated in CD patients vs. normal subjects), (2) genes differentially expressed in responders (R) and non-responders (NR) at baseline, and (3) ustekinumab treatment effects on the disease profile following induction and maintenance and potential difference in responders vs. non-responders.

The pharmacogenomics sub-study included N=88 patients who underwent ileocolonoscopy and provided mucosal biopsy samples (N=574) from both inflamed (I) and non-inflamed (NI) regions of the colon as well as ileum at 3 different time points (baseline, Week 6, and Week 22). Participation in this study was optional. Additionally, biopsies (N=14 colon and N=14 ileum) were obtained from normal subjects who were not enrolled in the C0743T26 study.

Ustekinumab treatment appears to modulate mRNA expression in inflamed colon and ileum, and in at least some patients, results in normalization of a fraction of dysregulated mRNAs. IL-12Rβ1 and IL-23A gene expression were modestly down regulated during the induction phase, but the change was not maintained during further treatment (See Table 3 in Appendix A). Any conclusions drawn from these results are limited due to the exploratory nature of the analysis and the following:

- These exploratory results are from a single study and have not been replicated,
- Data are available from only 17% of the patients included in the study. For some paired comparisons (Table 2 in Appendix A), meaningful interpretation of the results is limited by an even smaller sample size. For example, for changes in IL-12RB1 and IL-23A mRNA expression, data is derived from N=26 patients at Week 6 compared to N=9 patients at Screening,
- Multiple ustekinumab dose groups are combined for analysis thus limiting the ability to draw conclusions on potential dose dependent pharmacodynamic effects, and
- Reported heterogeneity among non-responders with respect to changes in the magnitude of expression of the transcripts at baseline.

2.10.3 Are the serum biomarker data and the tissue mRNA data from the Phase 2b and Phase 3 clinical trials in CD adequate for inclusion in the product labeling?

No, the serum biomarker and tissue mRNA data from the clinical trials are not adequate for inclusion in the product labeling. (b) (4)

The Clinical Pharmacology reviewer's comments on the serum biomarker analysis are described in Section 2.10.2.

Given the exploratory nature of the expression analysis and its limited use to inform prescribers, the Genomics Group Reviewer also concluded that the results are considered premature to be included in labelling. See Appendix B for further information.

3. LABELING

The clinical pharmacology related labeling changes, the sections in which the changes were proposed, and the acceptability of the changes are summarized in Table 23.

Table 23. Summary of labeling changes

Section	Major Proposed Labeling Revision/Addition	Acceptable
2.1 Dosing	(b) (4)	No, see Section 2.4
6.2 Immuno-genicity	In Crohn's disease clinical studies, less than 3% of patients treated with STELARA® developed antibodies to ustekinumab. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen. No ustekinumab-related serious hypersensitivity reactions were observed in psoriasis, and psoriatic arthritis and Crohn's disease clinical (b) (4)	Yes, see Section 2.6.4.2
12.1 Mechanism of Action	(b) (4)	No, see Section 2.10.2 and Appendix B
12.2 Pharmaco-dynamics		No, see Section 2.10.2 and Appendix B
12.3 Pharmaco-kinetics		No, see Section 2.5.8

4. APPENDIX A

OFFICE OF CLINICAL PHARMACOLOGY

GENOMICS GROUP REVIEW

BLA Number	761044
Submission Date	11/25/2015
Applicant Name	Janssen Biotech, Inc.
Generic Name	Ustekinumab
Proposed Indication	Moderately to severely active Crohn's disease
Primary Reviewer	Anuradha Ramamoorthy, Ph.D.
Secondary Reviewer	Christian Grimstein, Ph.D.

1 Background

The proposed indication for ustekinumab is treatment of patients with moderately to severely active Crohn's disease (CD) who have failed or were intolerant to immunomodulators or corticosteroids but never failed (b) (4) or failed or were intolerant to (b) (4) Ustekinumab was approved in 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis.

CD is a heterogeneous disease in which lesions can frequently occur in a background of normal mucosa with patchy and segmental inflammation along the gastrointestinal tract. IL-12, IL-23, and other cytokines play an important role in the pathogenesis of CD, as well as a number of autoimmune diseases [PMID: 26121196, 23114581, 16374252]. Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit that is used by both IL-12 and IL-23 that are involved in inflammatory and immune responses. The purpose of this review is to evaluate the pharmacodynamic (PD) effect of ustekinumab on the expression of mRNAs (including IL-12 and IL-23) in normal and CD tissues (colon and ileum), and whether labeling changes, or additional pharmacogenetic studies are indicated on the basis of these results.

2 Submission contents related to genomics

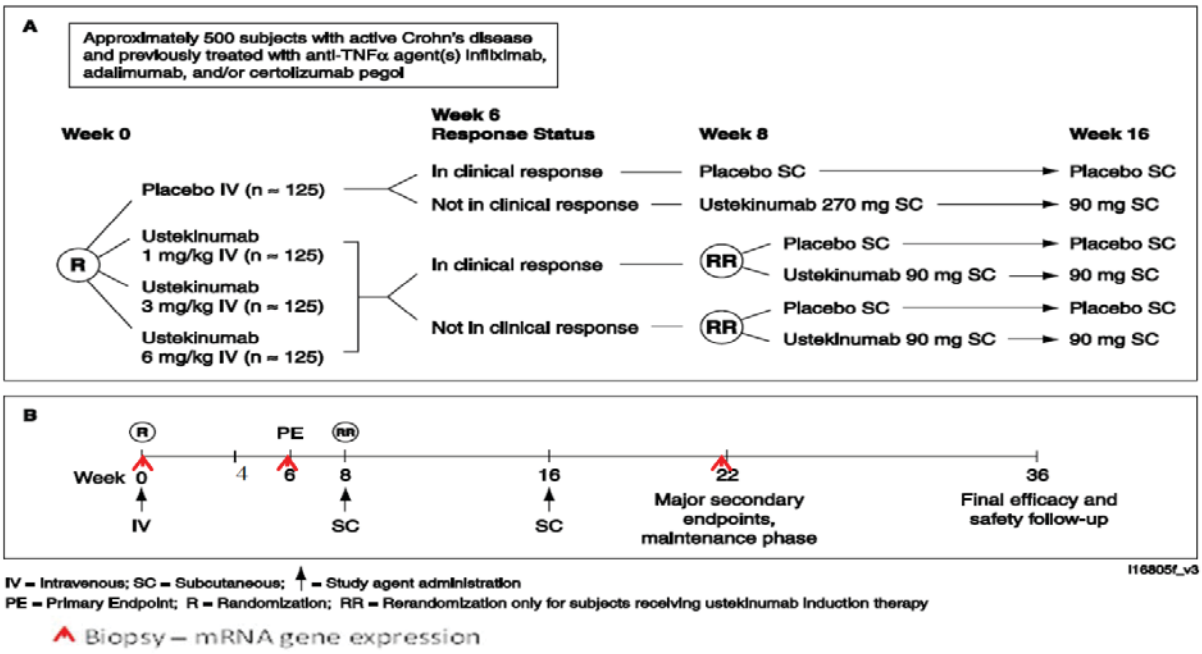
To perform pharmacodynamic analyses, the Applicant collected mRNA data in one Phase 2B study (Table 1 and Figure 1).

Table 1: Study evaluating the pharmacodynamic effect of ustekinumab on mRNA expression

Study name	Design	Dose/ Regimen	Objective	mRNA sampling rate (%)
C0743T26	Multicenter, randomized, double blind, placebo-controlled, parallel group, dose-ranging study in patients (≥ 18 years) with moderately to severely active CD previously treated with TNF antagonist therapies	Ustekinumab or Placebo (IV/SC); Drug administration at Week 0, 8, and 16 and follow-up at Week 36	Efficacy and safety	88/526 (17%)

Note: CD = Crohn's disease; IV = intravenous; SC = subcutaneous; TNF = tumor necrosis factor.

Figure 1: C0743T26 study schema



Source: Applicant's C0743T26 Biomarker Data Analyses Technical Report.

3 Key Question and Summary of Findings

3.1 Does treatment with ustekinumab result in pharmacodynamic (PD) changes in mRNA expression?

One of the secondary objectives of Study C0743T26 was to explore the pharmacodynamics of ustekinumab therapy, including effect of treatment on tissue mRNA expression. Analyses were performed to identify: (1) disease profile (colonic or ileal genes modulated in CD patients vs. normal subjects), (2) genes differentially expressed in responders (R) and non-responders (NR) at baseline, and (3) ustekinumab treatment effects on the disease profile following induction and maintenance therapy, and potential difference in responders vs. non-responders.

3.1.1 Study subjects and sampling

The optional pharmacogenomics ileocolonoscopy sub-study included N=88 patients who provided mucosal biopsy samples (N=574) from both inflamed (I) and non-inflamed (NI) regions of the colon as well as ileum at 3 different time points (baseline, Week 6, and Week 22). Additionally, biopsies (N=14 colon and N=14 ileum) were obtained from normal subjects (University of Pennsylvania School of Medicine, Philadelphia, PA) who were not a part of the C0743T26 study.

***Reviewer's comment**: In this study, evaluation of gene expression was performed as an exploratory analysis. As the pharmacogenomics sub-study was optional, data are available from only a small subset (17%) of the patients. No additional information is available on the phenotype of the tissues from 'normal' subjects.*

3.1.2 Methodology

RNA preparation: Total RNA was reported to be isolated with miRNAeasy kit following the manufacturer's instructions (Qiagen Inc., Valencia, CA).

Microarray analysis: Affymetrix GeneChip HT HGU133 + PM 96-Array plates (Affymetrix, Santa Clara, CA) and Array Studio software version 8.0 (OmicSoft Corp., St. Morrisville, NC) were used for analysis. In addition to the 28 normal colon and ileum samples, 535 of the 574 CD colon and ileum samples (excluding 8 samples that failed to generate microarray data and 31 additional samples that were identified by the Applicant as outliers using multiple QC procedures) were included in the subsequent data analysis. General Linear Model (GLM) of log-transformed data was used for statistical analysis to identify: (1) disease profile, (2) treatment effects, and (3) transcriptomic differences in response. For data analysis, a false discovery rate (FDR) was applied for multiple testing corrections and an adjusted p-value <0.05 was considered to be statistically significant. For disease profile, >2-fold significant differential expression and least squares means (LSMeans) >5.5 in at least one of the two conditions being compared was utilized for analysis. For treatment effect analysis, a >1.5-fold differential expression, along with an adjusted p-value <0.2 were utilized, and for and R/NR analysis, a >2-fold differential expression along with an adjusted p-value <0.1 were utilized. Subjects were analyzed by response status (i.e., Crohn's Disease Activity Index (CDAI) score drop from baseline). For the responder vs. non-responder analysis, the Applicant defined response status as follows:
(1) Induction (CDAI drop at Week 8 from Baseline) - non-responder (NR): 0-50, partial responder (PR): 50-100, responder (R): 100 and above (including super responder (SR)), and SR: 150 and above, and
(2) Maintenance (CDAI drop at Week 8/22 from Baseline) - persistent R: wk8R_wk22R, persistent NR: wk8NR_wk22NR, and remission (RM): wk8SR_wk22RM (sample size was reported to be too small for analysis).
The pathway analysis was performed using Ingenuity Pathway Analysis software (Qiagen, Redwood City, CA).

3.1.3 Results

3.1.3.1 *Disease profile of Crohn's disease*

To identify the transcript level disease profile, the Applicant compared the normal, CD colon, and CD illeal baseline biopsies. As shown in Table 2, a larger subset of transcripts was dysregulated when inflamed tissues (colon (N=1231) or ileum (N=603)) from patients were compared with biopsies from normal subjects. However, only a small subset of transcripts was dysregulated when non-inflamed tissues (colon (N=40) or ileum (N=66)) from patients were compared with biopsies from normal subjects (Table 2). When comparing the disease profile of inflamed colon vs. ileum, 296 of the 1538 dysregulated transcripts overlapped. The top canonical pathways similarly enriched in CD colon and ileum included granulocyte/agranulocyte adhesion and diapedesis, B-cell development, IL-17 signaling, and LXR/FXR/RXR activation. Per the Applicant, the results were consistent with the known pathophysiology reported for CD, including alterations in immune activations and recruitment (IL-6, IL-8, CXCL1), host-microbe interaction (DEFB4, DEFA6, TLR2), epithelial barrier function (XBP1, CLDN8), and solute transport (SLC6A14, AQP9).

Table 2: Number of transcripts differentially expressed between different subgroups

Comparisons	# of transcripts modulated
Differential mRNA transcript expression in CD colon and ileum compared to normal *	
Colon Inflamed area (N=54) vs. Normal (N=14)	1231
Colon Non-inflamed area (N=78) vs. Normal (N=14)	40
Ileum Inflamed area (N=49) vs. Normal (N=14)	603
Ileum Non-inflamed area (N=30) vs. Normal (N=14)	66
Differential mRNA transcript expression of inflamed vs. non-inflamed colon and ileal tissue at baseline, Week 6, and Week 22 *	
Screening: Colon Inflamed area (N=54) vs. Non- inflamed (N=78)	144
Week 6: Colon Inflamed area (N=42) vs. Non-inflamed area (N=81)	79
Week 22: Colon Inflamed area (N=33) vs. Non-inflamed area (N=62)	80
Screening: Ileum Inflamed area (N=49) vs. Non-inflamed area(N=30)	362
Week 6: Ileum Inflamed area (N=35) vs. Non-inflamed area (N=23)	262
Week 22:Ileum Inflamed area (N=27) vs. Non-inflamed area (N=21)	16
Ustekinumab treatment effects **	
Induction therapy treatment effects in colon	
PBO: NR Week 6 (N=8) vs. Screening (N=4)	324
PBO: R Week 6 (N=4) vs. Screening (N=3)	74
Ust: NR Week 6 (N=22) vs. Screening (N=20)	2209
Ust: R Week 6 (N=26) vs. Screening (N=9)	1049
Maintenance therapy treatment effects in colon	
Ust_Placebo: NR_NR Week 22 (N=4) vs. Screening (N=4)	1
Ust_Placebo: R_R Week 22 (N=5) vs. Screening (N=2)	0
Ust_Ust: NR_NR Week 22 (N=4) vs. Screening (N=6)	743
Ust_Ust: R_R Week 22 (N=13) vs. Screening (N=7)	605
Induction therapy treatment effects in ileum	
NR Week 6 (N=7) vs. Screening (N=16)	612
PR Week 6 (N=4) vs. Screening (N=7)	0
R Week 6 (N=9) vs. Screening (N=14)	1060
SR Week 6 (N=6) vs. Screening (N=7)	926
Maintenance therapy treatment effects in ileum	
Ust_Placebo: NR_NR Week 22 (N=3) vs. Screening (N=6)	0
Ust_Placebo: R_R Week 22 (N=1) vs. Screening (N=2)	25
Ust_Ust: NR_NR Week 22 (N=1) vs. Screening (N=3)	124
Ust_Ust: R_R Week 22 (N=8) vs. Screening (N=9)	494
Baseline differentiation of ustekinumab Week 8 responders and non-responders ***	
Inflamed area: Colon R (N=9) vs. NR (N=14)	365
Non-involved area: Colon R (N=17) vs. NR (N=14)	0
Inflamed area: Ileum R (N=14) vs. NR (N=11)	0
Non-involved area: Ileum R (N=8) vs. NR (N=5)	0

Source: Modified from C0743T26 Biomarker Data Analyses Technical Report. CD = Crohn's disease, PBO = placebo, NR = non-responder, R = responder, SR = super responder, N = number of patients in the different subgroups; * Differential expression was defined as a >2x change with false discovery rate (FDR) adjusted p-value <0.05 and LSMean >5.5; ** FC >1.5x and adjusted p-value <0.2; *** FC >2x and adjusted p-value <0.1.

3.1.3.2 *Inflamed versus non-inflamed tissue comparisons*

To assess changes in mRNA expression, inflamed and non-inflamed tissue were compared at baseline, as well as, post-treatment at Weeks 6 and 22. The differences between inflamed vs. non-inflamed tissue were reported to be more pronounced in the ileum than in the colon, and was largest at baseline (N=362 and 144 transcripts, respectively) but reduced following treatment at Weeks 6 (N=262 and 79 transcripts, respectively) and 22 (N=16 and 80 transcripts, respectively) (Table 2).

3.1.3.3 *Ustekinumab treatment effects in colon and ileum*

The Applicant reported that in both colon and ileum, when inflamed post-treatment samples were compared to inflamed baseline samples, no consistent significant treatment effects were reported during ustekinumab induction or maintenance therapy.

In the colon, ustekinumab treatment was reported to have a larger effect on the transcriptiome in both responders and non-responders when compared to placebo responders. According to the Applicant, in responders, about 25% (311/1231) transcripts of the disease profile were reported to be significantly normalized by ustekinumab treatment. When non-inflamed post-treatment samples were compared to inflamed baseline samples, changes in mRNA expression were reported for both induction and maintenance phases (Table 2). Of interest, during the induction phase, the expression of IL-12RB1 and IL-23A mRNAs were numerically down regulated in responders in non-inflamed post-treatment colon sample (N=9 patients) when compared to inflamed baseline colon sample (N=26 patients) (Table 3). This down regulation was not reported in the maintenance phase, or in non-responders, or in patients treated with placebo.

Table 3: Colon induction treatment effects in ustekinumab responders Week 6 vs. Screening

Probe set ID	Fold change	FDR p-value	Gene symbol	Gene name
1552584_PM_at	-1.8982	0.048	IL12RB1	interleukin 12 receptor, beta 1
239522_PM_at	-1.5824	0.0883	IL12RB1	interleukin 12 receptor, beta 1
210915_PM_x_at	-1.6163	0.1465	IL23A /// TRBV19	Interleukin 23, alpha subunit p19 /// T cell receptor beta

Source: C0743T26 Biomarker Data Analyses Technical Report. FDR = false discovery rate.

In the ileum, in responders, about 57% (312/603) transcripts of the disease profile were reported to be significantly normalized by ustekinumab treatment. Patients treated with ustekinumab were assessed for the differences between non-inflamed post-treatment ileum vs. baseline inflamed ileum and 1060 and 926 transcripts were different in responders and super-responders, respectively between Week 6 and baseline.

The top canonical pathway including, granulocyte/agranulocyte adhesion and diapedesis, IL-17 signaling modulated by ustekinumab treatment in ileum and colon are similar to that of the Crohn's disease profile (see section 3.1.3.1).

3.1.3.4 *Baseline differentiation of ustekinumab Week 8 responders and non-responders*

As shown in Table 2, according to the Applicant, 365 transcripts significantly differentiate ustekinumab Week 8 (all doses combined; N=9) and non-responders (excluding 1 mg/kg dose; N=14) in inflamed colon at baseline. No baseline expression differences between ustekinumab Week 8 responders and non-responders in non-inflamed colon or ileum were reported. Matrix metalloproteases, leukocyte extravasation signaling, and integrin signaling were some of the canonical pathways differentially expressed between responder vs. non-responder at baseline. Of note, gene expression may be also modulated by other factors, such as baseline inflammation burden (as measured by fecal calprotectin (<850 mg/g) and/or lactoferrin (<100 mg/g)).

Reviewer's comment: *Based on the Applicant's analyses, ustekinumab treatment appears to modulate mRNA expression in inflamed colon and ileum, and in at least some patients, results in normalization of a fraction of dysregulated mRNAs. Ustekinumab binds to the p40 protein subunit used by both IL-12 and IL-23. Hence, changes in the expression of these two cytokines may be expected. However, any conclusions drawn from these results are limited because of the following factors:*
(1) These exploratory results are from a single study and have not been replicated,
(2) Data are available from only 17% of the patients included in the study. For some paired comparisons (Table 2), meaningful interpretation of the results is limited by an even smaller sample size. For example, for changes in IL-12RB1 and IL-23A mRNA expression, data are derived from N=26 patients at Week 6 compared to N=9 patients at Screening,
(3) Multiple ustekinumab dose groups are combined for analysis thus limiting the ability to draw conclusions on potential dose-dependent pharmacodynamic effects, and
(4) Reported heterogeneity among non-responders with respect to changes in the magnitude of expression of the transcripts at baseline.

4 Summary and Conclusions

In this submission, the Applicant explored the PD effect of ustekinumab on the expression of mRNA in a Phase 2B study (C0743T26). Ustekinumab treatment appears to modulate mRNA expression in inflamed colon and ileum tissue, and results in normalizing mRNA expression in at least some patients. Consistent with the mechanism of action of ustekinumab, an IL-12 and IL-23 inhibitor, IL-12RB1 and IL-23A gene expression were down regulated during the induction phase (Table 3), but only modestly, and this was not maintained during further treatment (i.e., maintenance phase). However, the results of the exploratory analysis are based on a single study with a small sample size. In conclusion, given the exploratory nature of the biomarker analysis and its limited use to inform prescribers, the results are considered premature to be included in labelling.

5 Recommendations

The submission is acceptable from a Genomics and Targeted Therapy Group perspective. Given the exploratory preliminary nature of the biomarker analysis, the product labelling should be modified to remove the proposed IL-12RB1 and IL-23A tissue mRNA pharmacodynamic effects.

5.1 Post-marketing studies

No post-marketing commitments or requirements are recommended at this time from the Genomics and Targeted Therapy Group's perspective.

5.2 Labeling recommendations

Please see integrated labeling recommendations in Section 3 of the Clinical Pharmacology review.

5. INDIVIDUAL STUDY SUMMARY

Study CNTO1275NAP1002 (Phase 1: PK comparability)

Title

- A Phase 1, Randomized, Open-label, Parallel-design Study to Compare Single-dose Pharmacokinetics of Intravenous Ustekinumab Delivered in 2 Different Liquid in Vial Formulations

Study period

- 02 June 2014 to 19 December 2014

Objectives

- **Primary Objective**:

To evaluate the pharmacokinetic (PK) comparability of 2 different liquid in vial (LIV) formulations of ustekinumab, 90 mg/mL and 5 mg/mL, when administered as a single IV dose of 6 mg/kg in healthy subjects.

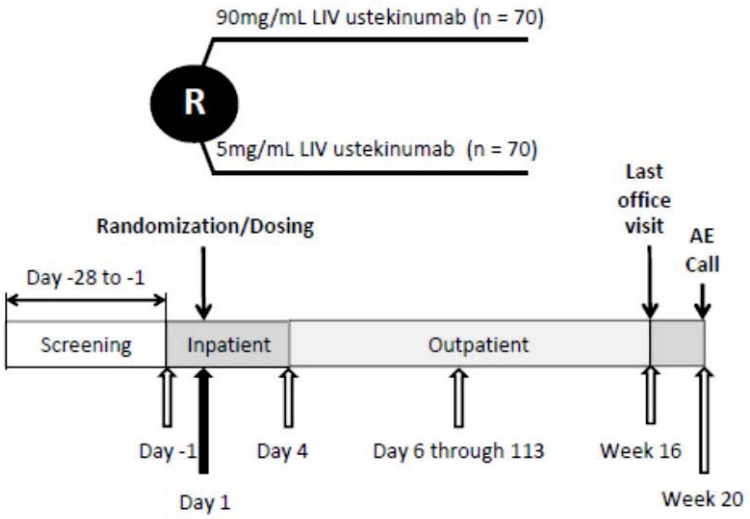
- **Secondary Objectives:**

To evaluate the safety, tolerability, and immunogenicity of a single IV administration of ustekinumab (6 mg/kg) in healthy subjects.

Study design

This was a multicenter randomized, parallel, open-label single-dose study in healthy subjects (Figure CNTO1275NAP1002-1).

Figure CNTO1275NAP1002-1. Study design. (*Data source: CSR CNTO1275NAP1002, Figure 1*)



AE = adverse event; LIV = liquid in vial; R = randomization

Test and reference treatment and dose administration

The *reference treatment* was a single 6 mg/kg IV infusion of ustekinumab 90 mg/mL (Group 1). The *test treatment* was a single 6 mg/kg IV infusion of ustekinumab 5 mg/mL (Group 2). In both the test and the reference groups, ustekinumab was administered as a constant rate IV infusion (using a pump) over 60 minutes.

Study population: disposition and demographics

Study subjects disposition:

- Number of subjects randomized: 140
- Number of subjects who completed: 137 subjects
- Number of subjects who discontinued: 3 subjects (Reference group)

Study subjects (randomized) baseline demographics:

- Sex: 61 men (43.6%) and 79 women (54.4%)
- Age: 35.1 ± 10.07 years (mean ± SD); range of 18 to 55 years
- Race: 104 (74.3%) white, 30 (21.4%) black or African American and 6 (4.2%) others
- Mean Body weight: 69.8 kg (90 mg/mL LIV formulation), 71.3 kg (5 mg/mL LIV formulation)

Study results

Pharmacokinetic Results:

The mean ± SD serum ustekinumab concentration-time profiles and forest plots of PK parameters (C_{max}, AUC_{last}, and AUC_{inf}) after a dose of 6 mg/kg administered as an infusion of a 90 mg/mL solution or 5 mg/mL solution are shown in Figure CNTO1275NAP1002-2. A summary of PK parameters is provided in Table CNTO1275NAP1002-1. Statistical evaluation of PK parameters between reference treatment and test treatment is provided in Table CNTO1275NAP1002-2.

Analysis of the PK data from this study demonstrated PK comparability between the two treatments (90 mg/mL and 5 mg/mL solutions of ustekinumab), as the 90% CIs for the ratio of the geometric least squares means for all 3 PK parameters (C_{max}, AUC_{last},and AUC_{inf}) were within the [0.8, 1.25] bioequivalence boundaries. Mean serum ustekinumab-time profiles were nearly superimposable between the 90 mg/mL and 5 mg/mL LIV formulations.

Immunogenicity and its impact on PK

Following a single dose of ustekinumab 6 mg/kg IV infusion, 2 of 139 subjects (1.4%, one in each treatment group) were positive for antibodies to ustekinumab. Ustekinumab half-life in these 2 subjects was shorter (11.7 and 17 days) than the mean half-life in the negative subjects (~25 days). Results didn't indicate a difference in the incidence of immunogenicity between the two ustekinumab formulations.

Figure CNTO1275NAP1002-2. Comparison of the Mean±SD serum ustekinumab concentration-time profiles and PK parameters (Cmax, AUClast, and AUCinf) after a dose of 6 mg/kg administered as an infusion of a 90 mg/mL solution (reference) or 5 mg/mL solution (test). (*Data source: CSR CNTO1275NAP1002, Figure 2*)

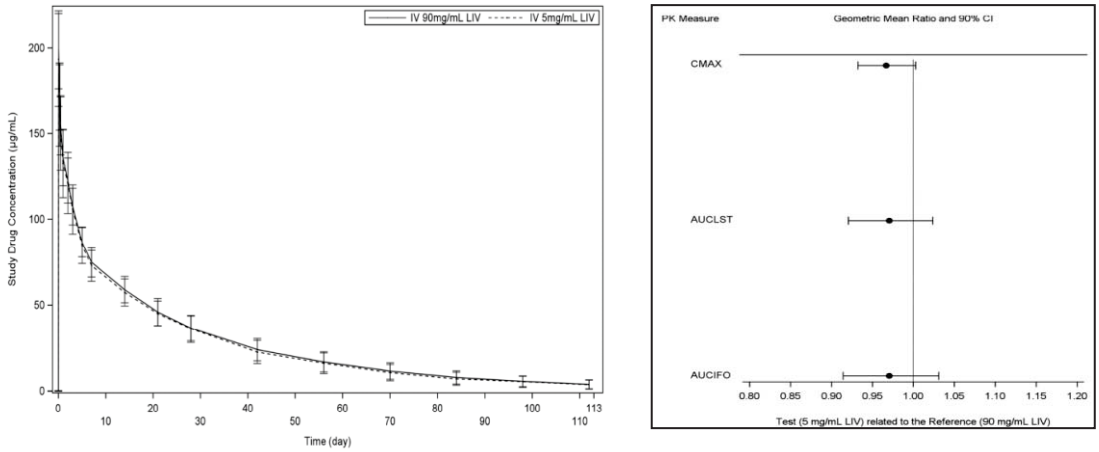


Table CNTO1275NAP1002-1. Summary of Ustekinumab PK parameter estimates (Cmax, AUClast, and AUCinf) after a dose of 6 mg/kg administered as an infusion of a 90 mg/mL solution (reference) or 5 mg/mL solution (test). (*Data source: CSR CNTO1275NAP1002, Table 3*)

Treatment	90 mg/mL solution (reference)			5 mg/mL solution (test)		
	C_{max} (mcg/mL)	AUC_{last} (day*mcg/mL)	AUC_{inf} (day*mcg/mL)	C_{max} (mcg/mL)	AUC_{last} (day*mcg/mL)	AUC_{inf} (day*mcg/mL)
N	69	67	68	69	69	68
Mean±SD	199 ±22.7	3052±542	3218±542	193±27.1	2970±574	3132±690
Median [range]	200 [158,251]	3132 [1840,4688]	3268 [1849, 5171]	197 [133, 247]	143 [6.53, 493]	3031 [1887, 5035]

Table CNTO1275NAP1002-2. Statistical evaluation of Ustekinumab PK parameters (Cmax, AUClast, and AUCinf) after a dose of 6 mg/kg administered as an infusion of a 90 mg/mL solution (reference) or 5 mg/mL solution (test). (Data source: CSR CNTO1275NAP1002, Table 3)

	Geometric mean		Geometric mean ratio (test/reference) and 90% confidence interval	
	90 mg/mL solution (reference)	5 mg/mL solution (test)		
Cmax (mcg/mL)	198	191	0.97	[0.93, 1.00]
AUC_{last} (day*mcg/mL)	3004	2916	0.97	[0.91, 1.03]
AUC_{inf} (day*mcg/mL)	3152	3060	0.97	[0.92, 1.02]

Study CNTO1275CRD3001 (Phase 3)

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 period

- 23 June 2011 to 03 July 2013

Objectives

Primary Objective:

- 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 pharmacodynamics biomarkers.

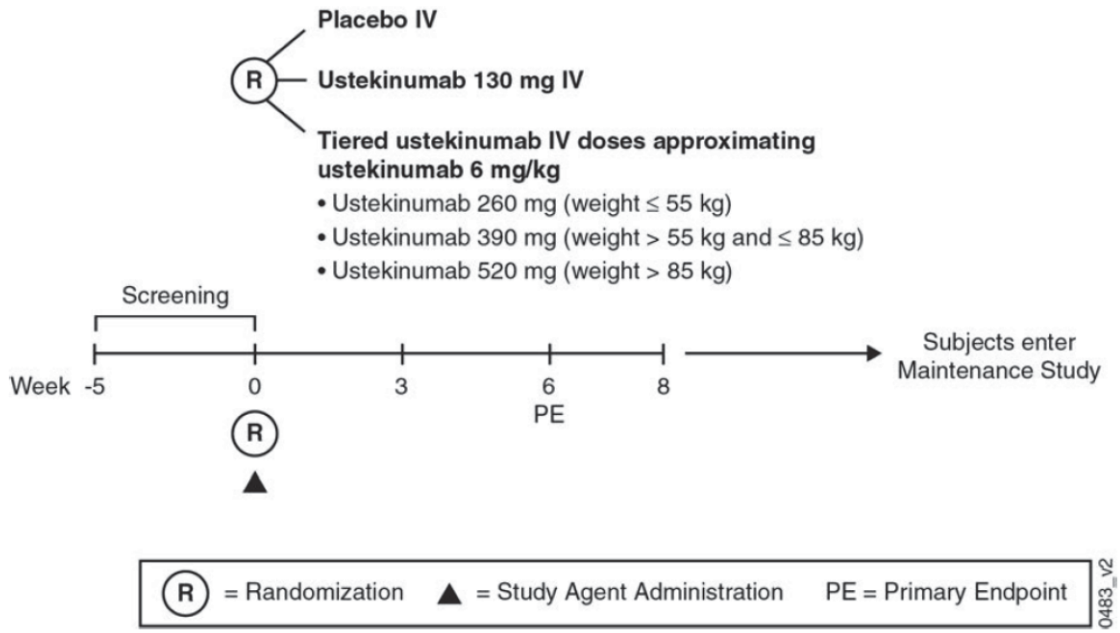
- To provide, along with induction study CNTO1275CRD3002, the target study population to be evaluated in the maintenance study CNTO1275CRD3003.

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects who have failed or are intolerant to one or more TNF antagonist therapies (Figure CNTO1275CRD3001-1). After initial screening, subjects were randomized in a 1:1:1 ratio at Week 0 to receive a single IV administration of either placebo or 1 of 2 induction doses of ustekinumab (ustekinumab 130 mg or tiered ustekinumab doses approximating ustekinumab 6 mg/kg. At Week 6, all subjects were 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.

Primary endpoint:
Primary endpoint was clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥100 points. Secondary endpoints were clinical remission at Week 8 (CDAI score <150 points), clinical response at Week 8, 70-point response at Week 6, defined as a reduction from baseline in the CDAI score of ≥70 points; and 70-point response at Week 3.

Figure CNTO1275CRD3001-1. Study design. (*Source: CSR CNTO1275CRD3001, Figure 1*)



Study Agent:
Ustekinumab liquid in vial (LIV) was presented as a 90 mg/mL solution in 2 mL single use vials with 2 dose strengths (90 mg in 1 mL nominal volume or 45 mg in 0.5 mL nominal volume).

Study duration:
Subjects were randomized at Week 0 to receive a single IV dose of placebo, 130 mg ustekinumab, or ~6 mg/kg ustekinumab at Week 0. Subjects were evaluated at Week 6 for the primary endpoint of clinical response and at Week 8, eligible subjects could enter the maintenance study, CNTO1275CRD3003.

Subjects
The sponsor had initially planned for 675 subjects (225 subjects per treatment group) for this study. Due to a stability issue associated with the batch of study agent, Sponsor temporarily suspended dosing of subjects and data from the 28 subjects dosed before suspension was excluded from the analysis. A total of 741 subjects were subsequently included in the study after the study was restarted (247 in the placebo group, 245 in the ustekinumab 130 mg group, and 249 in the ustekinumab ~6 mg/kg group).

Immunogenicity

Blood samples for immunogenicity assessment were collected at Week 0 (pre- and postinfusion) and Week 6 (and at an early termination visit if necessary).

Pharmacokinetics

In all subjects, blood samples for ustekinumab PK assessment were collected at at Week 0 (before and approximately 1 hour after the completion of the infusion), and at Weeks 3, 6, and 8 (or at the early termination visit).

Study results

Analysis of clinical response

Table CNTO1275CRD3001-1 and Table CNTO1275CRD3001-2 summarizes clinical response at week 6 (primary end point) and week 8 across the study groups in this study. For the primary end point (week 6), the response rate in both the ~6 mg/kg (33.7%) and 130 mg (34.3%) ustekinumab groups were significantly greater (p=0.003 and p=0.002, respectively) compared to the placebo group (21.5%). The proportion of subjects in clinical response at week 8 was also significantly greater in both the ~6 mg/kg (37.8%) and 130 mg (33.5%) ustekinumab groups compared with the placebo group (20.2%; p<0.001 and p=0.001, respectively).

Table CNTO1275CRD3001-1. Proportion of subjects in clinical response at Week 6. (*Data source: CSR CNTO1275CRD3001, Table 6)*

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.

Table CNTO1275CRD3001-2. Proportion of subjects in clinical response at Week 8. (*Data source: CSR CNTO1275CRD3001, Table 8)*

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

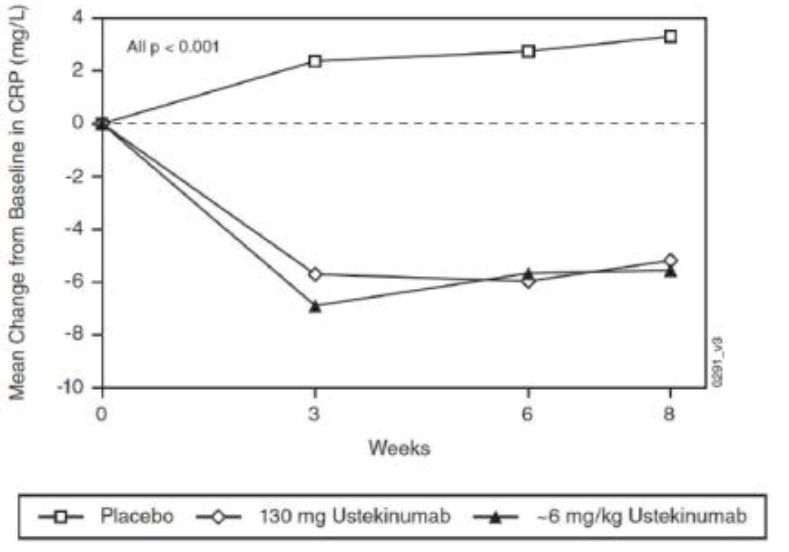
		Ustekinumab		
	Placebo	130 mg	6 mg/kg[a]	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494
Week 8				
N	247	245	249	494
Subjects in clinical response[b,c]	50 (20.2%)	82 (33.5%)	94 (37.8%)	176 (35.6%)
p-value		0.001	< 0.001	< 0.001

[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.

Pharmacodynamics

Mean CRP concentrations at baseline in the ustekinumab groups were slightly higher in the ~6 mg/kg and 130 mg ustekinumab groups (19.50 and 19.96 mg/L, respectively) compared with the placebo group (16.56 mg/L). However, significant reductions in CRP levels from baseline were observed at weeks 3, 6 and 8 in both ustekinumab treated groups compared with the placebo group (Figure CNTO1275CRD3001-2).

Figure CNTO1275CRD3001-2. Mean Change from Baseline in CRP Concentration (mg/L) through Week 8 (*Data source: CSR CNTO1275CRD3001, Figure 8)*



[a] Subjects who, prior to the designated analysis timepoint, had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes, had their baseline value carried forward.
[b] Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward.

Data source: [TEFCRP02.rtf] [CNTO1275\CRD3001\DBR_W8_W20\RE_W8_W20\tefcrp02.sas] 16AUG2013, 16:01

Pharmacokinetics

Table CNTO1275CRD3001-3 summarizes the serum ustekinumab concentrations through week 8 following a single IV administration of 130 mg or ~6 mg/kg ustekinumab. Figure CNTO1275CRD3001-2 summarizes median serum ustekinumab concentrations through Week 8. In comparing across the two dose groups, the median serum ustekinumab concentrations were approximately dose proportional at all timepoints through Week 8.

Table CNTO1275CRD3001-3. Summary of Serum Ustekinumab Concentrations (micrograms/mL) through Week 8 (*Data source: CSR CNTO1275CRD3001, Table 3)*

	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.

Within the group of subjects receiving the tiered dose of 6 mg/kg, median serum ustekinumab concentrations at all timepoints through Week 8 tended to be higher as the absolute ustekinumab dose increased (Table CNTO1275CRD3001-4). Median serum ustekinumab concentrations at Week 6 were 6.95 µg/mL, 10.15 µg/mL, and 12.08 µg/mL in subjects receiving the 260 mg, 390 mg, and 520 mg dose, respectively. Similarly at Week 8, median serum ustekinumab concentrations were 3.87 µg/mL, 6.55 µg/mL, and 8.76 µg/mL in subjects receiving the 260 mg, 390 mg, and 520 mg doses, respectively.

Table CNTO1275CRD3001-4. Summary of Serum Ustekinumab Concentrations (micrograms/mL) by Weight-range Based Dose Category (*Data source: CSR CNTO1275CRD3001, Table 4)*

	Ustekinumab 6mg/kg		
	260 mg	390 mg	520 mg
Analysis set: Treated subjects who received weight-range based ustekinumab dose approximating 6 mg/kg excluding those enrolled prior to study re-start[a]	56	144	45
Weight (kg)			
N	56	144	45
Mean (SD)	49.71 (6.901)	67.79 (8.205)	101.23 (17.368)
Median	49.60	66.80	94.50
IQ range	(45.75; 53.05)	(60.30; 74.00)	(88.90; 109.00)
Range	(35.0; 89.0)	(55.1; 87.9)	(85.2; 172.8)
Week 0, preadministration			
N	56	143	45
Mean (SD)	0.01 (0.050)	0.04 (0.375)	0.01 (0.043)
Median	0.00	0.00	0.00
IQ range	(0.00; 0.00)	(0.00; 0.00)	(0.00; 0.00)
Range	(0.0; 0.2)	(0.0; 4.4)	(0.0; 0.3)
Week 0, 1 hour postadministration			
N	55	136	45
Mean (SD)	101.06 (16.691)	136.76 (25.148)	147.03 (33.998)
Median	102.30	134.09	145.93
IQ range	(86.13; 113.50)	(118.81; 155.43)	(128.14; 162.37)
Range	(63.2; 142.3)	(66.6; 213.5)	(16.3; 224.8)
Week 3			
N	48	135	40
Mean (SD)	15.73 (6.915)	26.45 (9.707)	29.40 (7.728)
Median	16.12	25.67	29.42
IQ range	(10.62; 21.38)	(17.71; 32.81)	(25.02; 34.06)
Range	(0.0; 31.7)	(9.9; 53.9)	(1.9; 46.5)
Week 6			
N	46	126	39
Mean (SD)	6.36 (4.203)	11.26 (5.982)	13.55 (4.593)
Median	6.95	10.15	12.08
IQ range	(2.50; 9.26)	(6.73; 15.59)	(10.67; 16.45)
Range	(0.2; 18.5)	(1.9; 32.1)	(5.8; 24.7)
Week 8			
N	33	98	29
Mean (SD)	4.22 (3.301)	7.07 (4.522)	8.93 (3.647)
Median	3.87	6.55	8.76
IQ range	(1.19; 6.22)	(3.32; 9.77)	(6.80; 10.27)
Range	(0.0; 13.4)	(0.5; 24.8)	(3.3; 17.2)

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

Immunogenicity

Out of the 484 ustekinumab-treated subjects, one subject (0.2%) was positive for antibodies to ustekinumab through the Week 6 visit and through the final safety visit. This subject was in the 130 mg group and was not on immunomodulators at baseline.

Study CNTO1275CRD3002 (Phase 3)

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 period

- 23 Jun 2011 to 28 Oct 2014

Objectives

Primary Objective:

- To evaluate the efficacy of IV induction regimens of ustekinumab in inducing clinical response in subjects with moderately to severely active Crohn's disease.
- To evaluate the safety of IV induction regimens of ustekinumab in subjects with moderately to severely active Crohn's disease.

Secondary Objectives:

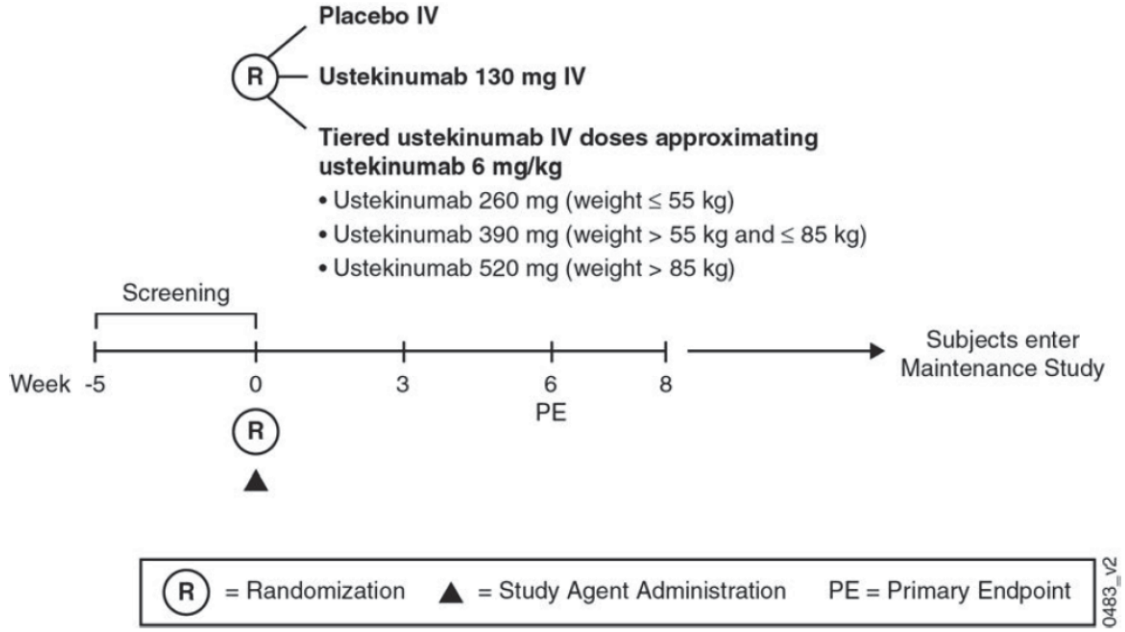
- To evaluate the efficacy of IV induction regimens of ustekinumab in inducing clinical remission.
- To evaluate the efficacy of IV induction regimens of ustekinumab in improving disease-specific health-related quality of life.
- To evaluate the pharmacokinetics and pharmacodynamics of ustekinumab therapy, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other pharmacodynamic biomarkers.
- To provide, along with induction study CNTO1275CRD3001, the target study population to be evaluated in the maintenance study CNTO1275CRD3003.

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study (Figure CNTO1275CRD3002-1). The target population was adult subjects with moderately to severely active Crohn's disease (of at least 3 months duration). These subjects had demonstrated an inadequate response to or failed to tolerate corticosteroids or immunomodulators (6-mercaptopurine [6-MP], azathioprine [AZA], and methotrexate [MTX]).

After initial screening, subjects were randomized in a 1:1:1 ratio at Week 0 to receive a single IV administration of either placebo or 1 of 2 induction doses of ustekinumab (ustekinumab 130 mg or tiered ustekinumab doses approximating ustekinumab 6 mg/kg). At Week 6, all subjects were 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.

Figure CNTO1275CRD3002-1. Study design. (*Source: CSR CNTO1275CRD3002, Figure 1*)



Primary endpoint:
Primary endpoint was clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥100 points. Secondary endpoints were clinical remission at Week 8 (CDAI score <150 points), clinical response at Week 8, 70-point response at Week 6, defined as a reduction from baseline in the CDAI score of ≥70 points; and 70-point response at Week 3.

Study Agent:
Ustekinumab liquid in vial (LIV) was presented as a 90 mg/mL solution in 2 mL single use vials with 2 dose strengths (90 mg in 1 mL nominal volume or 45 mg in 0.5 mL nominal volume).

Study duration:
Subjects were randomized at Week 0 to receive a single IV dose of placebo, 130 mg ustekinumab, or ~6 mg/kg ustekinumab at Week 0. Subjects were evaluated at Week 6 for the primary endpoint of clinical response and at Week 8, eligible subjects could enter the maintenance study, CNTO1275CRD3003.

Subjects
The sponsor had initially planned for 600 subjects (200 subjects per treatment group) for this study. Due to a stability issue associated with the batch of study agent, Sponsor temporarily suspended dosing of subjects and data from the 12 subjects dosed before suspension was excluded from the analysis. A total of 628 subjects were subsequently included in the study after the study was restarted (210 in the placebo group, 209 in the ustekinumab 130 mg group, and 209 in the ustekinumab ~6 mg/kg group). group. Data for 1 subject was retrospectively excluded from the efficacy analyses because the Sponsor was unable to determine the accuracy and validity of the subject's data due to Good Clinical Practice concerns identified at the study site.

Immunogenicity

Blood samples for immunogenicity assessment were collected at Week 0 (pre- and postinfusion) and Week 6 (and at an early termination visit if necessary).

Pharmacokinetics

In all subjects, blood samples for ustekinumab PK assessment were collected at at Week 0 (before and approximately 1 hour after the completion of the infusion), and at Weeks 3, 6, and 8 (or at the early termination visit).

Study results

Analysis of clinical response

Table CNTO1275CRD3002-1 and Table CNTO1275CRD3002-2 summarizes clinical response at week 6 (primary end point) and week 8 across the study groups in this study. For the primary end point (week 6), the response rate in both the ~6 mg/kg (55.5%) and 130 mg (51.7%) ustekinumab groups were significantly greater ($p < 0.001$) compared to the placebo group (28.7%). The proportion of subjects in clinical response at week 8 was also significantly greater in both the ~6 mg/kg (57.9%) and 130 mg (47.4%) ustekinumab groups compared with the placebo group (32.1%; $p<0.001$).

Table CNTO1275CRD3002-1. Proportion of subjects in clinical response at Week 6. (*Data source: CSR CNTO1275CRD3002, Table 6)*

		Ustekinumab		
	Placebo	130 mg	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 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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Table CNTO1275CRD3002-2. Proportion of subjects in clinical response at Week 8. (*Data source: CSR CNTO1275CRD3002, Table 8)*

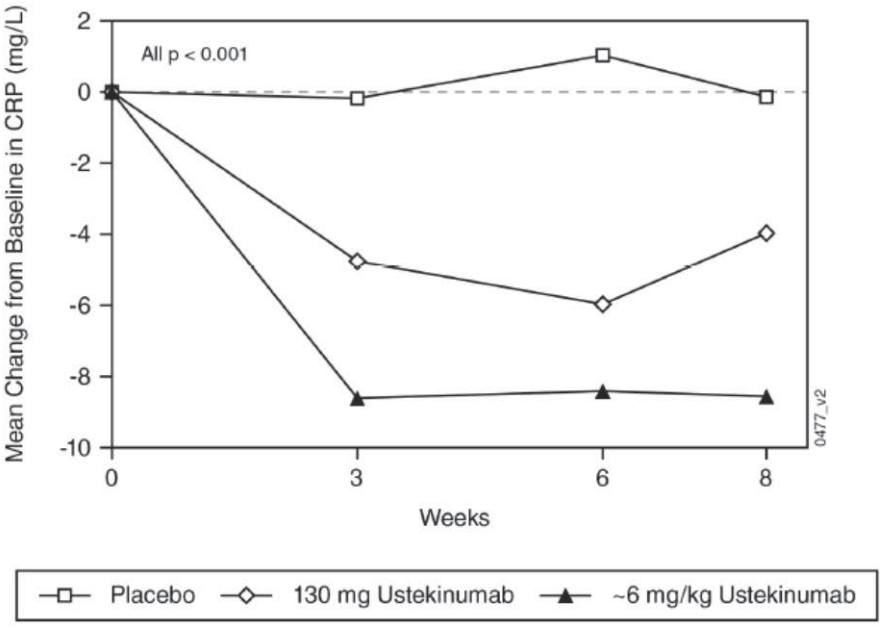
	Placebo	Ustekinumab		
		130 mg	6 mg/kg[a]	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start and excluding site 1127	209	209	209	418
Week 8				
N	209	209	209	418
Subjects in clinical response[b,c]	67 (32.1%)	99 (47.4%)	121 (57.9%)	220 (52.6%)
p-value		< 0.001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

Pharmacodynamics

Mean reductions in CRP concentrations were seen in both the ~6 mg/kg and 130 mg ustekinumab groups compared with placebo at each timepoint ($p<0.001$ for both groups). Additionally, at all timepoints, the magnitude of reduction was greater for the high dose compared to the low dose ustekinumab group (Figure CNTO1275CRD3002-2).

Figure CNTO1275CRD3002-2. Mean Change from Baseline in CRP Concentration (mg/L) through Week 8 (*Data source: CSR CNTO1275CRD3002, Figure 8)*



[a] Subjects who, prior to the designated analysis timepoint, had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes, had their baseline value carried forward.
[b] Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward.

Pharmacokinetics

Table CNTO1275CRD3002-3 summarizes the serum ustekinumab concentrations through week 8 following a single IV administration of 130 mg or ~6 mg/kg ustekinumab. In comparing across the two dose groups, the median serum ustekinumab concentrations were approximately dose proportional at all timepoints through Week 8.

Table CNTO1275CRD3002-3. Summary of Serum Ustekinumab Concentrations (micrograms/mL) through Week 8 (*Data source: CSR CNTO1275CRD3002, Table 3)*

	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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Within the group of subjects receiving the tiered dose of 6 mg/kg, median serum ustekinumab concentrations at all timepoints through Week 8 tended to be higher as the absolute ustekinumab dose increased (Table CNTO1275CRD3002-4). Median serum ustekinumab concentrations at Week 6 were 9.1 µg/mL, 10.0 µg/mL, and 13.1 µg/mL in subjects receiving the 260 mg, 390 mg, and 520 mg dose, respectively. Similarly at Week 8, median serum ustekinumab concentrations were 5.3 µg/mL, 6.4 µg/mL, and 8.3 µg/mL in subjects receiving the 260 mg, 390 mg, and 520 mg doses, respectively.

Table CNTO1275CRD3002-4. Summary of Serum Ustekinumab Concentrations (micrograms/mL) by Weight-range Based Dose Category (*Data source: CSR CNTO1275CRD3002, Table 4)*

	Ustekinumab 6mg/kg		
	260 mg	390 mg	520 mg
Analysis set: Treated subjects who received weight-range based ustekinumab dose approximating 6 mg/kg excluding those enrolled prior to study re-start[a]	40	123	43
Weight (kg)			
N	40	123	43
Mean (SD)	48.01 (5.337)	70.54 (8.794)	98.21 (15.293)
Median	49.35	71.00	93.40
IQ range	(44.05; 52.75)	(63.50; 78.00)	(88.70; 103.40)
Range	(35.0; 55.0)	(55.4; 85.9)	(86.0; 154.0)
Week 0, preadministration			
N	40	122	43
Mean (SD)	0.06 (0.324)	0.01 (0.049)	0.06 (0.359)
Median	0.00	0.00	0.00
IQ range	(0.00; 0.00)	(0.00; 0.00)	(0.00; 0.00)
Range	(0.0; 2.0)	(0.0; 0.4)	(0.0; 2.3)
Week 0, 1 hour postadministration			
N	40	117	42
Mean (SD)	101.47 (23.798)	120.17 (36.473)	140.69 (25.420)
Median	100.43	122.82	138.05
IQ range	(86.15; 116.10)	(105.32; 139.29)	(128.35; 156.63)
Range	(44.2; 161.2)	(0.0; 199.9)	(70.7; 215.5)
Week 3			
N	39	112	41
Mean (SD)	18.52 (7.644)	26.14 (11.786)	31.36 (8.663)
Median	19.86	25.31	32.36
IQ range	(14.23; 23.59)	(17.86; 33.51)	(24.16; 37.72)
Range	(0.0; 33.7)	(0.0; 72.7)	(15.8; 49.7)
Week 6			
N	35	111	36
Mean (SD)	8.70 (4.463)	11.99 (8.067)	13.90 (6.135)
Median	9.10	9.97	13.12
IQ range	(5.93; 11.33)	(6.62; 15.69)	(8.60; 18.36)
Range	(0.5; 17.6)	(0.0; 45.0)	(4.5; 27.1)
Week 8			
N	26	92	25
Mean (SD)	5.06 (2.618)	7.34 (5.247)	8.16 (3.877)
Median	5.26	6.39	8.30
IQ range	(3.31; 6.70)	(3.38; 9.76)	(4.31; 10.29)
Range	(0.3; 10.1)	(0.0; 24.6)	(2.6; 17.3)

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

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Immunogenicity

Out of the 411 ustekinumab-treated subjects with appropriate samples for the assessment of antibodies to ustekinumab, one subject (0.2%) was positive for antibodies to ustekinumab through the Week 6 visit and through the final safety visit. This subject was in the 130 mg group and was not taking immunomodulators at baseline.

Study CNTO1275CRD3003 (Phase 3)

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 period

- 13 September 2011 to 10 June 2015;

Objectives

Primary Objective:

- 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, and 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 (PK), immunogenicity, and pharmacodynamics (PD) of ustekinumab therapy, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other PD biomarkers; and to evaluate the effect of ustekinumab on health-related quality of life (QOL).

Study design

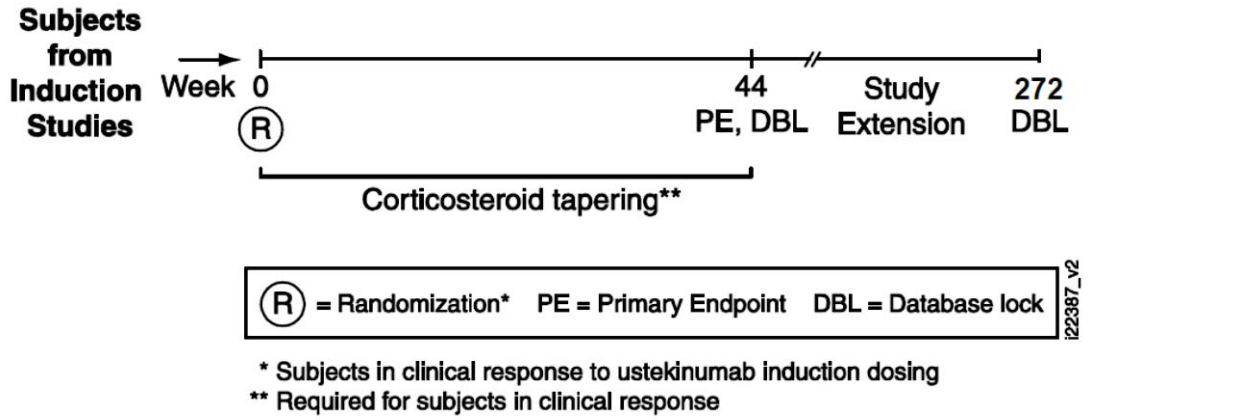
This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with moderately to severely active Crohn's disease induced into clinical response with ustekinumab in induction studies CNTO1275CRD3001 or CNTO1275CRD3002 (Figure CNTO1275CRD3003-1).

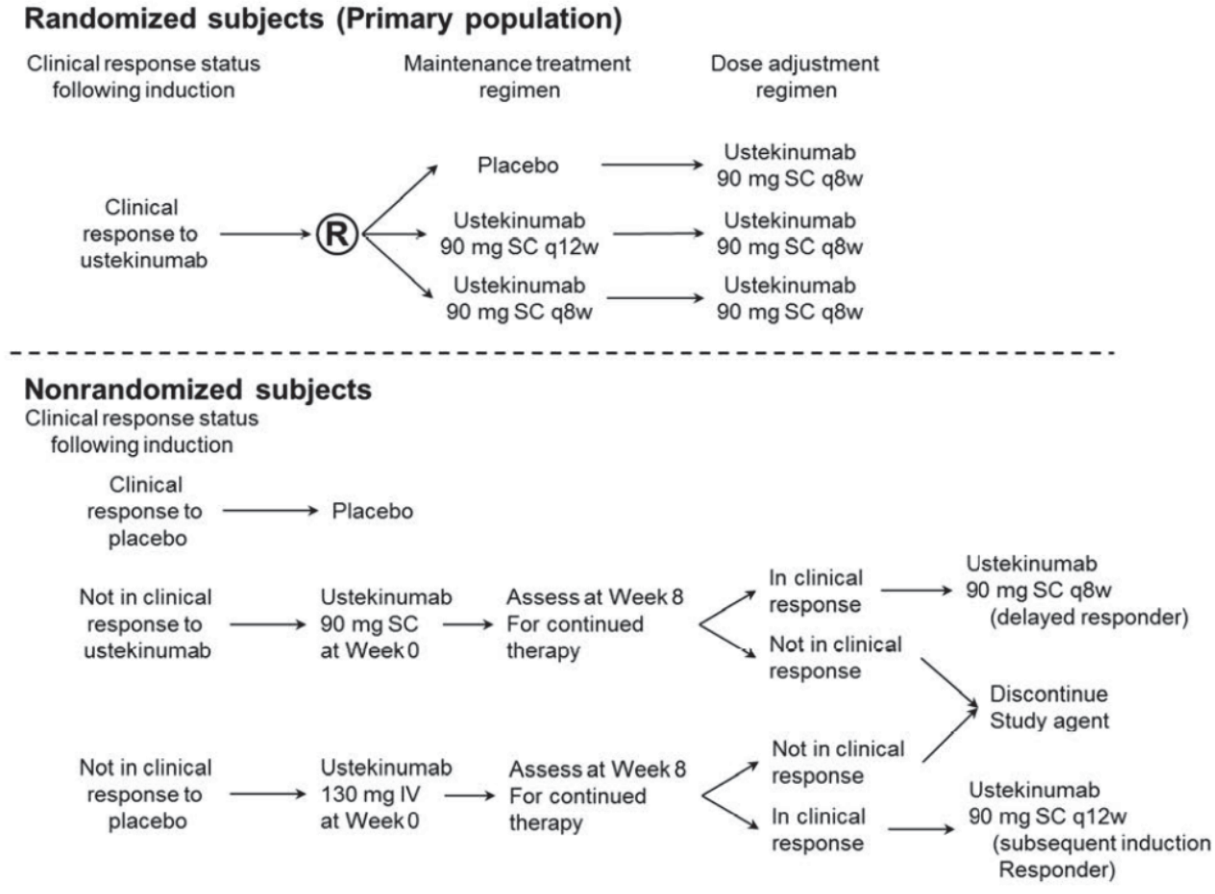
The responders in induction studies CNTO1275CRD3001 or CNTO1275CRD3002 were the primary population for this study. These subjects were randomized in a 1:1:1 ratio at Week 0 to receive a SC administration of either placebo or 1 of 2 maintenance regimens of ustekinumab (90 mg every 12 weeks [q12w] through Week 36 or ustekinumab 90 mg every 8 weeks [q8w] through Week 40).

Subjects who were not in clinical response to ustekinumab at Week 8 of the induction studies, as well as all subjects who initially received placebo (both in clinical response and not in clinical response), were also eligible to enter the study, but were not included in the primary population. Subjects in clinical response to placebo intravenous (IV) induction continued to

receive SC placebo throughout the maintenance study. Subjects not in clinical response to IV placebo induction received ustekinumab 130 mg IV administration at Week 0.

Figure CNTO1275CRD3003-1. Study design. (*Source: CSR CNTO1275CRD3003, Figure 1 and 2*)





Primary and secondary endpoints:
Primary endpoint was clinical remission at Week 44, defined as a CDAI score of <150 points. Secondary endpoints included:

- Clinical response at Week 44, defined as a reduction from Week 0 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 in the CDAI score of ≥100 points.
- Clinical remission at Week 44 among subjects in clinical remission to ustekinumab at Week 0 of maintenance.
- 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 (i.e., subjects from induction study CNTO1275CRD3001).

Study Agent:
Ustekinumab liquid in vial (LIV) was presented as a 90 mg/mL solution in a single-use prefilled syringe (PFS) containing 1 mL of ustekinumab.

Study duration:
Duration of treatment in the main study was 44 weeks. The long-term extension continues through Week 272.

Subjects
The sponsor had initially planned for 1275 subjects for this study. Due to a stability issue associated with the batch of study agent, Sponsor temporarily suspended dosing of subjects and data from the subjects dosed before suspension (9 randomized subjects and 17 nonrandomized subjects) was excluded from the analysis.
A total of 1,281 subjects who completed the ustekinumab induction studies were subsequently included in the study.
397 subjects (31.0%) were in the primary population (i.e. were in clinical response to ustekinumab IV induction at Week 8; randomized subjects). These were divided as follows:

- 133 subjects randomized to placebo
- 132 subjects randomized to ustekinumab 90 mg q12w
- 132 subjects randomized to ustekinumab 90 mg q8w

884 subjects (69.0%) were enrolled but not randomized (i.e. nonrandomized subjects). These were divided as follows:

- 285 placebo induction nonresponders who received an ustekinumab 130 mg IV infusion at Week 0.
- Subjects who achieved clinical response by Week 8 of maintenance continued to receive ustekinumab 90 mg q12w (subsequent induction responders).
- 476 ustekinumab induction nonresponders who received ustekinumab 90 mg at Week 0.
- Subjects who achieved clinical response by Week 8 of maintenance continued to receive ustekinumab 90 mg q8w (delayed responders).

Immunogenicity

Blood samples for immunogenicity assessment were collected at Week 0 and at Weeks 12, 24, 36, and 44 (and at an early termination visit if necessary).

Pharmacokinetics

In all subjects, blood samples for ustekinumab PK assessment were collected at Week 0 (before and approximately 1 hour after the completion of the infusion), and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44 (or at the early termination visit).

Study results

Analysis of clinical response in primary subjects

Table CNTO1275CRD3003-1 summarizes clinical remission rates at week 44 (primary end point) across the subjects in the primary analysis population in this study. For the primary end point (week 44), the remission rate in both the 90 mg q8w (53.1 %) and q12w (48.8 %) ustekinumab groups were significantly greater (p=0.005 and p=0.04 for the q8w and q12w groups, respectively) compared to the placebo group (35.9 %).

Table CNTO1275CRD3003-1. Proportion of subjects in clinical remission at Week 44. (*Data source: CSR CNTO1275CRD3003, Table 5)*

		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.

The proportions of subjects in clinical remission over time were generally similar for the ustekinumab 90 mg q12w and q8w groups with separation from the ustekinumab groups observed by Week 20 (Figure CNTO1275CRD3003-2). 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).

Figure CNTO1275CRD3003-2. Proportion of subjects in clinical remission at each visit through Week 44. (*Data source: CSR CNTO1275CRD3003, Figure 7)*

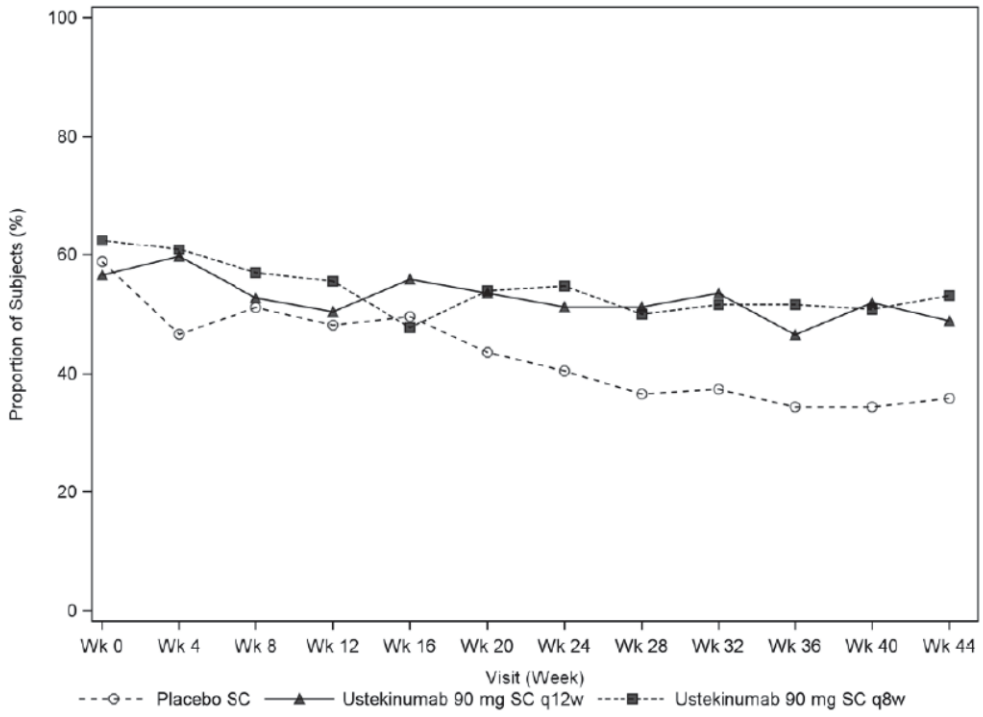


Table CNTO1275CRD3003-2 summarizes clinical response rates at weeks 36, 40 and 44 across the subjects in the primary analysis population in this study. The proportions of subjects in sustained clinical response were significantly greater in the ustekinumab 90 mg q12w and q8w groups (53.5% and 53.1%, respectively) compared with the placebo group (38.2%; p=0.019 for both the q12w and q8w comparisons).

Of the subjects randomized to placebo, 51 subjects were initiated into ustekinumab 90 mg q8w regimen after meeting loss of response criteria (LOR). At assessments 16 weeks after initiation of maintenance therapy, 39.2% of these subjects were in clinical remission and 70.6% of these subjects had regained clinical response.

In the subjects randomized to ustekinumab 90 mg q12w group, 29 subjects had a dose adjustment to 90 mg q8w after meeting LOR criteria. At assessment 16 weeks after dose adjustment, 41.4% of these subjects were in clinical remission and 55.2% of these subjects had regained clinical response.

In the subjects randomized to ustekinumab 90 mg q8w group, 28 subjects met LOR criteria for dose adjustment but continued to receive ustekinumab 90 mg q8w. At assessment 16 weeks after dose adjustment, 32.1% of these subjects were in clinical remission and 46.4% of these subjects had regained clinical response.

Table CNTO1275CRD3003-2. Proportion of subjects in clinical response at Weeks 36, 40 and 44. (*Data source: CSR CNTO1275CRD3003, Table TEFCRES09)*

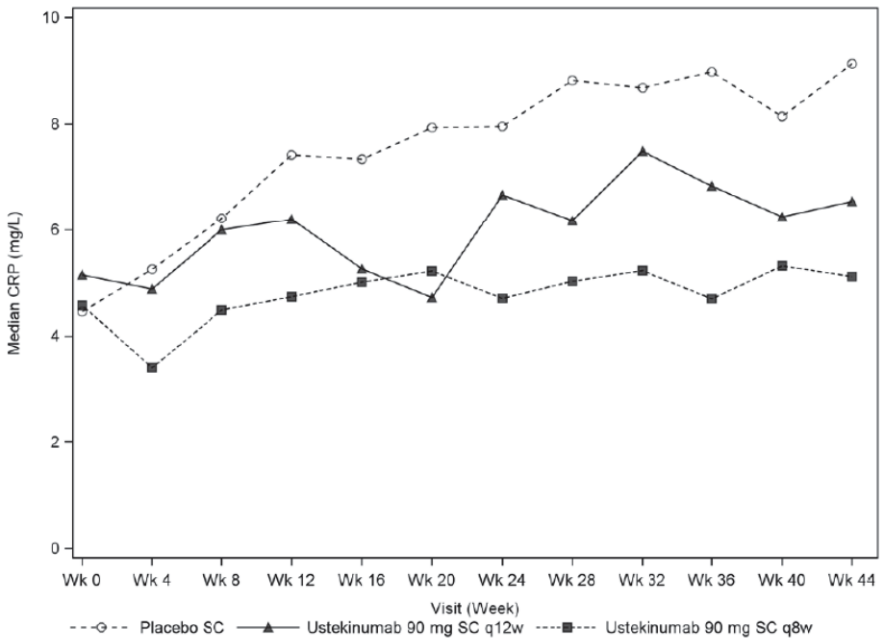
		ustekinumab		
	placebo SC[a]	90 mg SC q12w	90 mg SC q8w	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128	257
Sustained clinical response				
N	131	129	128	257
Subjects in sustained clinical response at Weeks 36, 40, and 44 [b,c]	50 (38.2%)	69 (53.5%)	68 (53.1%)	137 (53.3%)
p-value		0.019	0.019	0.007

[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 timepoints 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 any of the designated analysis timepoints are considered not to be in clinical response.

Pharmacodynamics

Median CRP in the placebo group increased over time with clear separation from the ustekinumab treated groups by week 44. The separation in median CRP between the q12w and placebo groups was lower over time relative to the q8w group, particularly from Week 24 through Week 44 (Figure CNTO1275CRD3003-3).

Figure CNTO1275CRD3003-3. Median Change from Baseline in CRP Concentration (mg/L) through Week 44 (*Data source: CSR CNTO1275CRD3003, Figure GEFCRP03)*

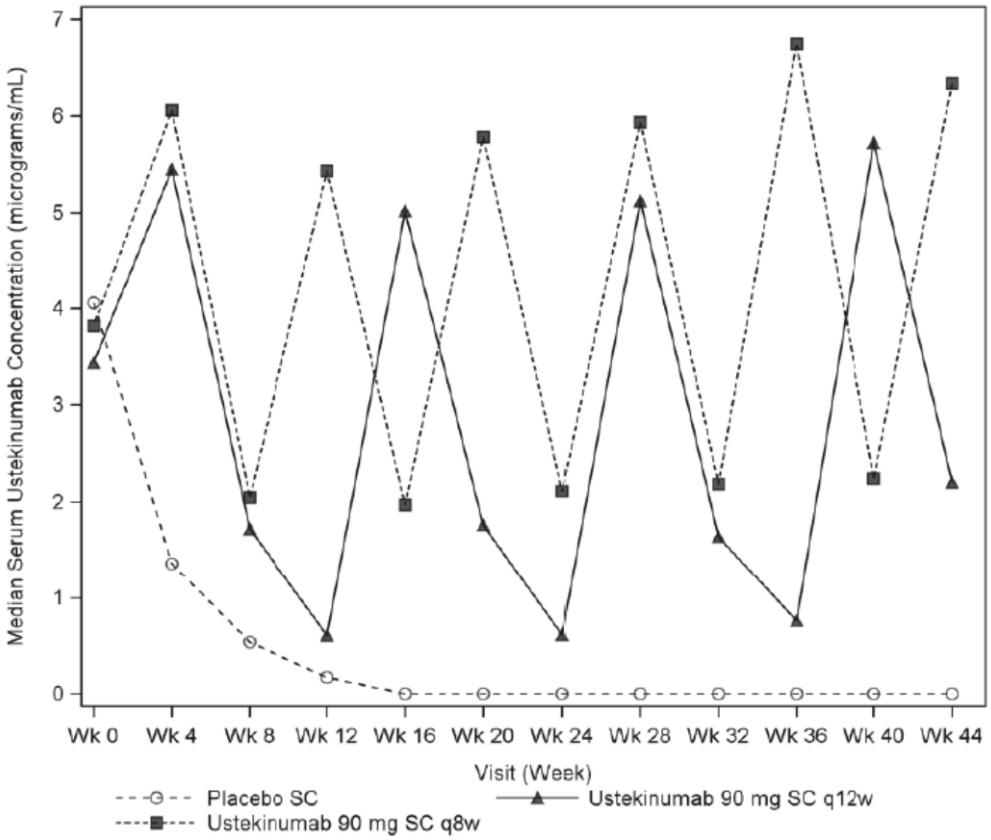


Pharmacokinetics

Figure CNTO1275CRD3003-4 illustrates median serum ustekinumab concentrations through week 44 following a maintenance dose of ustekinumab 90 mg SC q12w or ustekinumab 90 mg q8w through Week 44. Before administration of the first SC maintenance dose at Week 0, median serum ustekinumab concentrations were comparable between subjects in the placebo, 90 mg q12w, and 90 mg q8w treatment groups.

As can be expected, by week 16 median serum concentration was below detectable limits in subjects randomized to placebo maintenance. In subjects randomized to usetekinumab treatment (q12w or q8w), median serum ustekinumab concentrations were maintained above detectable limits through Week 44. In the ustekinumab 90 mg q8w group, median pre-administration serum ustekinumab concentrations from Week 8 through Week 44 ranged from 1.97 µg/mL to 2.24 µg/mL. In the ustekinumab 90 mg q12w group, median pre-administration serum ustekinumab concentrations from Week 8 through Week 44 ranged from 0.61 µg/mL to 0.76 µg/mL. At Week 44, median serum ustekinumab concentrations were 6.34 µg/mL in the ustekinumab 90 mg q8w, and 2.20 µg/mL in the ustekinumab 90 mg q12w group.

Figure CNTO1275CRD3003-4. Median serum ustekinumab concentrations (micrograms/mL) through Week 44 (*Data source: CSR CNTO1275CRD3003, Figure 5)*



Serum ustekinumab concentrations tended to be lower in subjects who met the LOR criteria for dose adjustment compared with those who did not meet the criteria. This was true across subjects randomized to the placebo group as well as subjects randomized to ustekinumab 90 mg q12w. In these subjects serum ustekinumab concentrations increased following dose adjustment from placebo or ustekinumab 90 mg q12w to ustekinumab 90 mg q8w.

Immunogenicity

Table CNTO1275CRD3003-3 summarizes the immunogenicity response during the maintenance study across all treated subjects (randomized and non-randomized groups). Of the 1,154 treated subjects assessed for antibodies for ustekinumab, 27 subjects (2.3%) were positive for antibodies to ustekinumab through Week 44 of this maintenance study (Table CNTO1275CRD3003-3). Of these 27 treated subjects who were positive for antibodies to ustekinumab, 17 (63.0%) were positive for neutralizing antibodies.

Of these 27 subjects, 14 (out of 396) were responders during the ustekinumab IV induction phase of the study; 9 (out of 474) were non-responders during the ustekinumab IV induction phase of the study who received ustekinumab in maintenance phase. Remaining (4 out of 284) were non-responders from the placebo arm of the IV induction phase who received ustekinumab in maintenance phase.

Table CNTO1275CRD3003-3. Summary of Antibody to ustekinumab status during this maintenance study through Week 44. (*Data source: CSR CNTO1275CRD3003, Table 4)*

		Non-responders to IV		
	Responders to ustekinumab IV induction dosing[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]	Total
Analysis set: Treated subjects who received a dose of ustekinumab either in induction or maintenance	396	285	476	1157
Subjects with appropriate samples [d]	396	284	474	1154
Subjects positive for antibodies to ustekinumab at any time during maintenance [e,f]	14 (3.5%)	4 (1.4%)	9 (1.9%)	27 (2.3%)
Titers				
1:50	1	0	1	2
1:100	6	0	0	6
1:200	0	1	3	4
1:400	4	1	1	6
1:800	1	0	1	2
1:1600	2	0	1	3
1:3200	0	0	1	1
1:6400	0	1	1	2
1:51200	0	1	0	1

Table CNTO1275CRD3003-4 summarizes the antibody to ustekinumab status during this maintenance study through Week 44 in subjects who were randomized and had a dose adjustment. In assessing the randomized subjects who met LOR criteria through week 44 and had a dose adjustment, 5 subjects (out of 109; 4.6%) were positive for antibodies to ustekinumab. On the other hand, in randomized subjects who didn't have dose adjustment 9 subjects (out of 287; 3.1%) were positive for antibodies to ustekinumab.

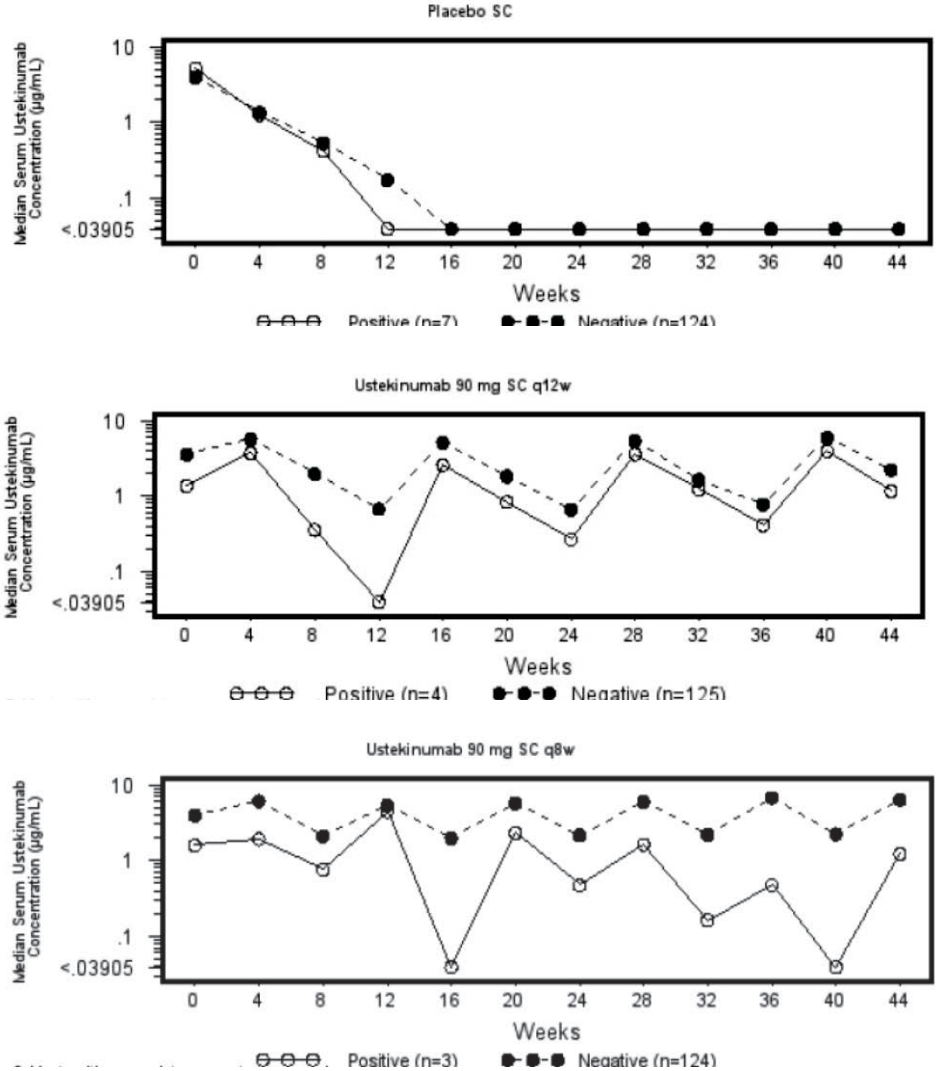
Table CNTO1275CRD3003-4. Summary of antibody to ustekinumab status during this maintenance study through Week 44 in subjects who were randomized and had a dose adjustment. (*Data source: CSR CNTO1275CRD3003, Table TPKIR02A)*

	placebo SC[a]	ustekinumab 90 mg SC q12w	ustekinumab 90 mg SC q8w	Combined	Total
Analysis set: Treated subjects who were randomized and had a dose adjustment	51	29	29	58	109
Subjects with appropriate samples [b]	51	29	29	58	109
Subjects positive for antibodies to ustekinumab at any time during maintenance [c,d]	3 (5.9%)	1 (3.4%)	1 (3.4%)	2 (3.4%)	5 (4.6%)
Titers					
1:50	1	0	0	0	1
1:100	1	0	0	0	1
1:200	0	0	0	0	0
1:400	1	1	1	2	3
1:800	0	0	0	0	0
1:1600	0	0	0	0	0
1:3200	0	0	0	0	0
1:6400	0	0	0	0	0
1:51200	0	0	0	0	0
Subjects negative for antibodies to ustekinumab during maintenance [c,e]	48 (94.1%)	28 (96.6%)	28 (96.6%)	56 (96.6%)	104 (95.4%)

[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 with appropriate samples had 1 or more evaluable samples obtained from induction Week 6 through maintenance Week 44.
[c] Denominator is number of subjects with appropriate samples.
[d] Includes all subjects who had at least 1 positive sample at any time from induction Week 6 through maintenance Week 44.
[e] Excludes subjects who were positive at any time from induction Week 6 through maintenance Week 44 and includes subjects whose samples may contain ustekinumab at the evaluation visit.

Figure CNTO1275CRD3003-5 highlights the relationship between serum ustekinumab concentrations and antibody to ustekinumab status in randomized subjects. Across all three groups (placebo, ustekinumab 90 mg q12w and ustekinumab 90 mg q8w), median serum ustekinumab concentrations were lower in subjects who were positive for antibodies to ustekinumab relative to subjects who were negative for antibodies to ustekinumab.

Figure CNTO1275CRD3003-5. Line plot of median serum ustekinumab concentrations (micrograms/mL) over time by antibody to ustekinumab status (*Data source: CSR CNTO1275CRD3003, Figure 6)*



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OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRICS REVIEW

BLA: **761044**	Submission Date: **November 25, 2015**
Drug Name	**Ustekinumab (STELARA®)**
Pharmacometrics Reviewer	**Jee Eun Lee, Ph.D.**
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Genomics and Targeted Therapy Reviewer	**Anuradha Ramamoorthy, Ph.D.**
Genomics and Targeted Therapy Team Leader	**Christian Grimstein, Ph.D.**
OCPB Division	**DPM/DCP3**
ORM division	**OND/ DGIEP**
Sponsor	**Janssen Biotech, Inc.**
Indication	**Treatment of moderate to severe Crohn's disease in patients who have failed/were (b) (4) to immunomodulators or (b) (4) TNF (b) (4) reatment**

This review is an addendum to the Clinical Pharmacology Review (Dr. Hon, dated to August 9, 2016).

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is weight based dosing adequate ustekinumab during induction phase?

Yes, it appears to be adequate for the studied population because of the following reasons.

- The placebo-adjusted clinical remission or clinical response does not provide clear evidence for lower efficacy in patients with lower body weight.
- The apparent lower exposures in patients with lower body weight do not appear to have an impact on clinical remission or clinical response.

The review team was concerned over potential underdosing of ustekinumab for patients weight ≤55 kg since the observed concentrations of ustekinumab at Week 3 and Week 6 appeared to be lower than those in patients weighing >55 kg who received higher doses while ustekinumab concentrations following 130 mg fixed dosing were comparable among the subgroups of body weight (Figure 1).

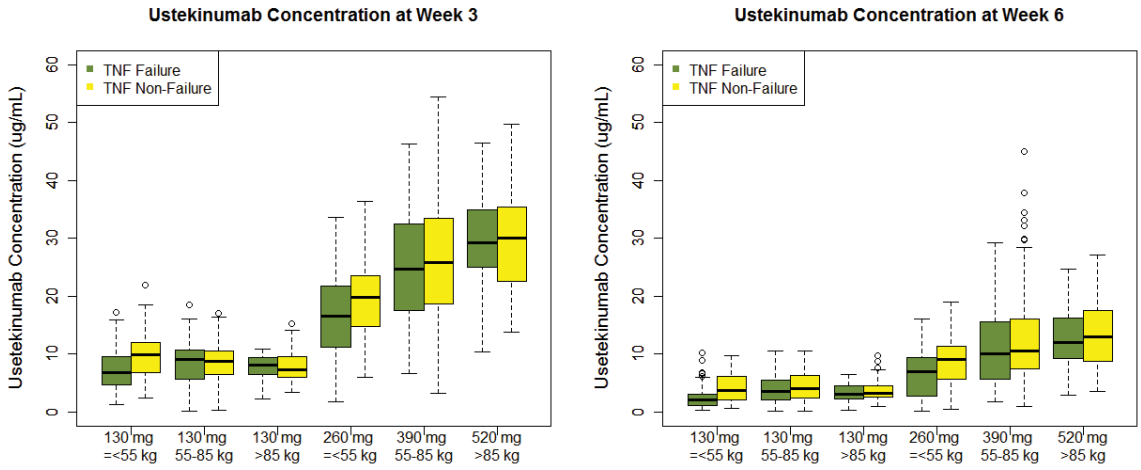


Figure 1. Exposures of Ustekinumab by Weight Group Following Body Weight Tired Dosing *(Source: Reviewer's analysis)*

Since the effect of body weight on ustekinumab clearance was estimated to be within ±20% from the population PK analysis (see Section 3.1), a weight-based dosing regimen for patients with Crohn's disease is less likely. Thus the adequacy of weight-tiered dosing was evaluated for efficacy. However, the review team was not able to find clear evidence for the effect of lower exposure of ustekinumab on the clinical response or clinical remission in the induction phase.

The efficacy rates were lower in patients weighing ≤55 kg with 260 mg dose compared to other weight groups of patients who received 390 mg and 520 mg for induction. Nonetheless, the response and remission rates following placebo in patients weighing ≤55 kg were also lower than those in patients weighing >55 kg. After adjustments with placebo effects, the concern was only remaining with clinical remission rate at Week 8: 8.1% following 260 mg in patients with TNF non-failure weighing ≤55 kg while 23.7% following 390 mg in those weighing 55-85 kg and 17.1% following 520 mg in those weighing >85 kg (Figure 3 (b)). However, the placebo-adjusted remission rate at Week 8 was 17.4% following 130 mg in these patients weighing ≤55 kg (Figure 3 (d)) although the exposures following 130 mg in patients weighing ≤ 55 kg were lower than the exposures in patients weighing ≤55 kg who received 260 mg (Figure 1).

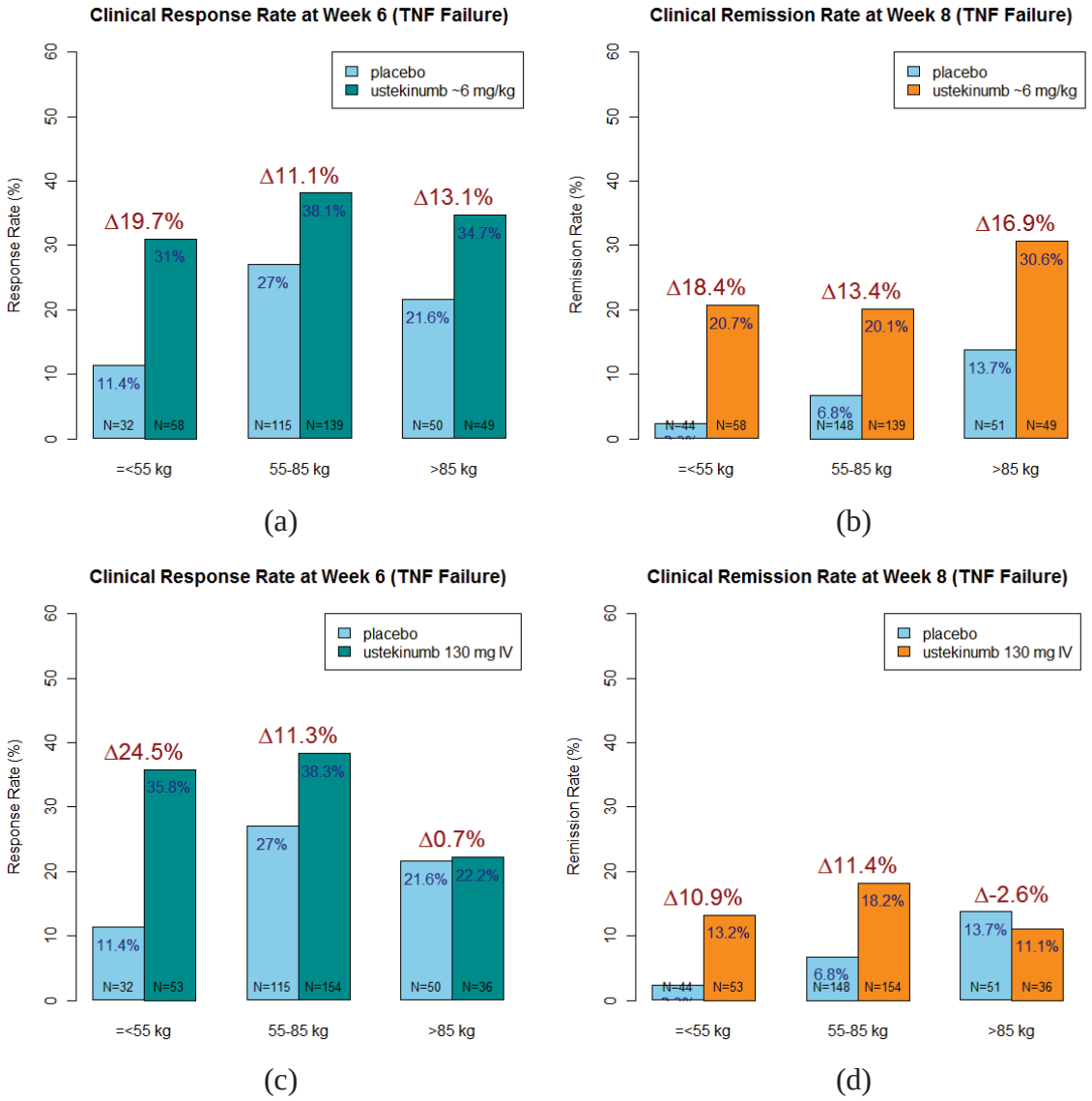


Figure 2. Clinical response at Week 6 and clinical remission at Week 8 in patients who failed to anti-TNFα therapy ((a) clinical response at Week 6 following ~6 mg/kg, (b) clinical remission at Week 8 following ~6 mg/kg, (c) clinical response at Week 6 following 130 mg, (d) clinical remission at Week 8 following 130 mg. Placebo-adjusted rates are in blue font) *(Source: Reviewer's analysis)*

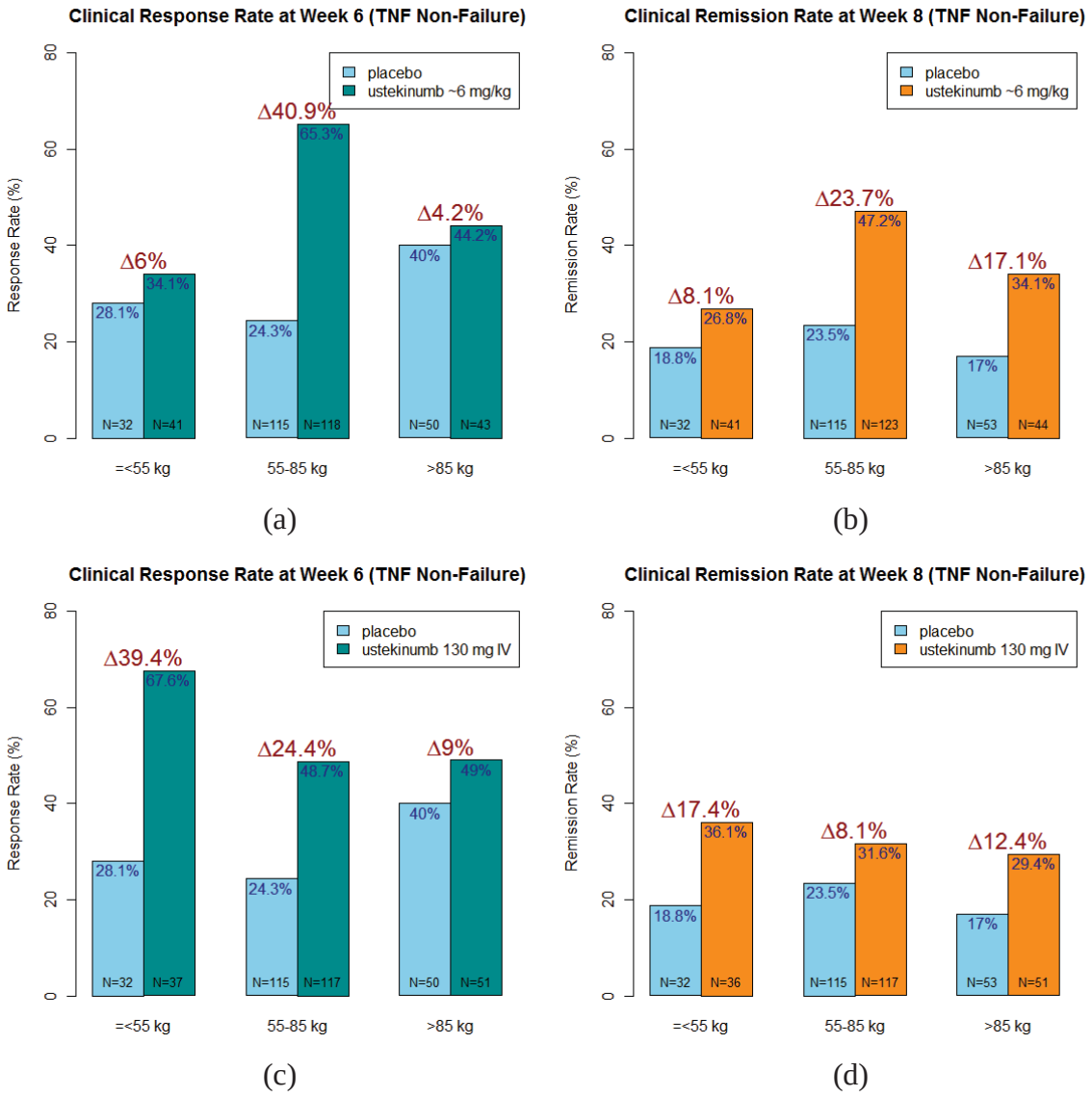


Figure 3. Clinical response at Week 6 and clinical remission at Week 8 in patients who had not failed to anti-TNFα therapy ((a) clinical response at Week 6 following ~6 mg/kg, (b) clinical remission at Week 8 following ~6 mg/kg, (c) clinical response at Week 6 following 130 mg, (d) clinical remission at Week 8 following 130 mg. Placebo-adjusted rates are in blue font) *(Source: Reviewer's analysis)*

The effect of lower induction rates in this group of patients does not seem to persist with continuous dosing of ustekinumab. The clinical remission rate at Week 44 (Week 52 referenced to Week 0 of induction phase) was higher than other weight groups of patients (Table 7 & Table 8). Furthermore, placebo-adjusted clinical response at Week 6 and placebo-adjusted clinical remission at Week 8 do not provide consistent evidence for lower efficacy possibly caused by lower exposures of ustekinumab. The lower efficacy following ~6 mg/kg dose in patients weighing≤ 55 kg might not be due to the lower exposures. There might be other unidentified confounding variables that caused lower remission rates in this subgroup since patients with lower body weight who received

placebo also showed lower response rate during the induction (Figure 2 & Figure 3). In summary, there is no clear evidence that the lower exposure of ustekinumab in the lower weight subgroups results in lower rates of efficacy.

1.1.2 Is there any benefit for approving both Q8W and Q12W dosing regimens in the label?

- Are there any baseline risk factors that may support the need for approving Q12W dosing regimen?

No. (b) (4) As shown in Table 1, while the trial was not powered to assess the dose-response relationship, the efficacy with Q8W dosing regimen is numerically higher than that with Q12W dosing regimen. A similar trend was observed for clinical remission in subgroups of patients; who are anti-TNFα refractory/intolerant, who failed conventional therapy but not anti-TNFα therapy or who are anti-TNFα naïve. (b) (4)

Table 1. Efficacy Results from Phase 3 Maintenance Study

	Placebo (N=131)	90 mg STELARA Q8W (N=128)	90 mg STELARA Q12W (N=129)
Clinical Remission	36%	53%	49%
Clinical Response	44%	59%	58%
Corticosteroid-Free Clinical Remission	30%	47%	43%
Sustained Clinical Remission	26%	46%	40%

(Source: SCE Table 5, page 59)

Thus, a potential effect of baseline disease characteristic was evaluated for body weight, sex, race, ethnicity, baseline methotrexate use, baseline antibiotics use and baseline use of any concomitant medication for CD management (Figure 4). Comparisons of these baseline disease characteristics between patients who received Q8W and those who received Q12W dosing regimen were also made (Figure 5). As shown in Figure 4 & Figure 5, disease characteristics appear to be evenly distributed between the two dose groups and no notable risk factors that predict response status were observed.

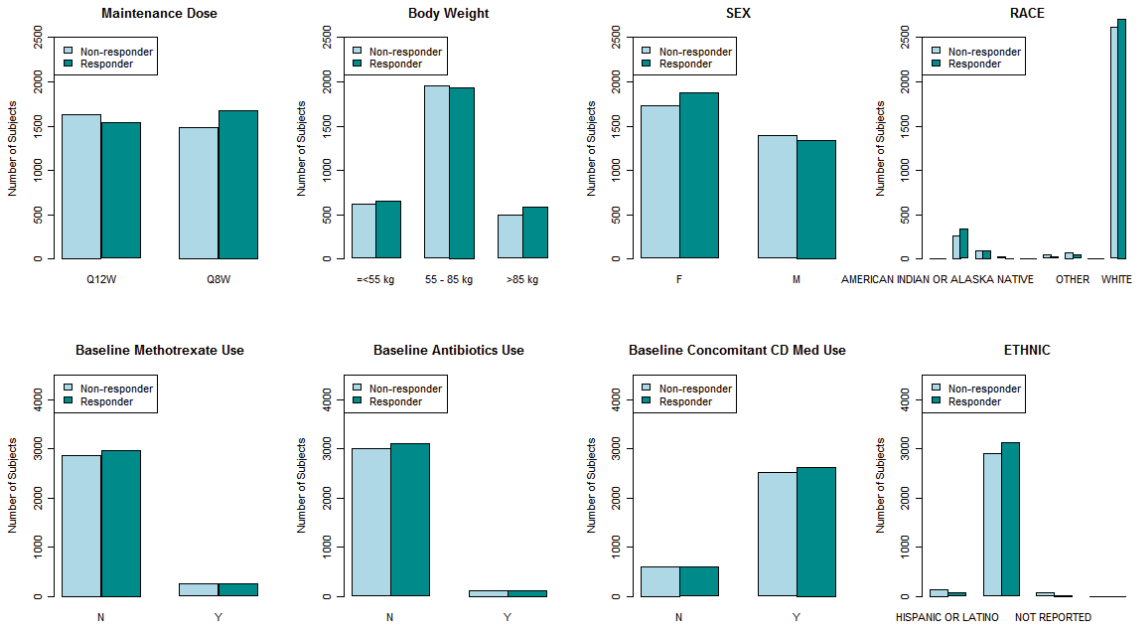


Figure 4. Baseline Disease Characteristics by Response Status for Clinical Remission at Week 44 (Week 52 referenced to Week 0 in Induction) *(Source: Reviewer's analysis)*

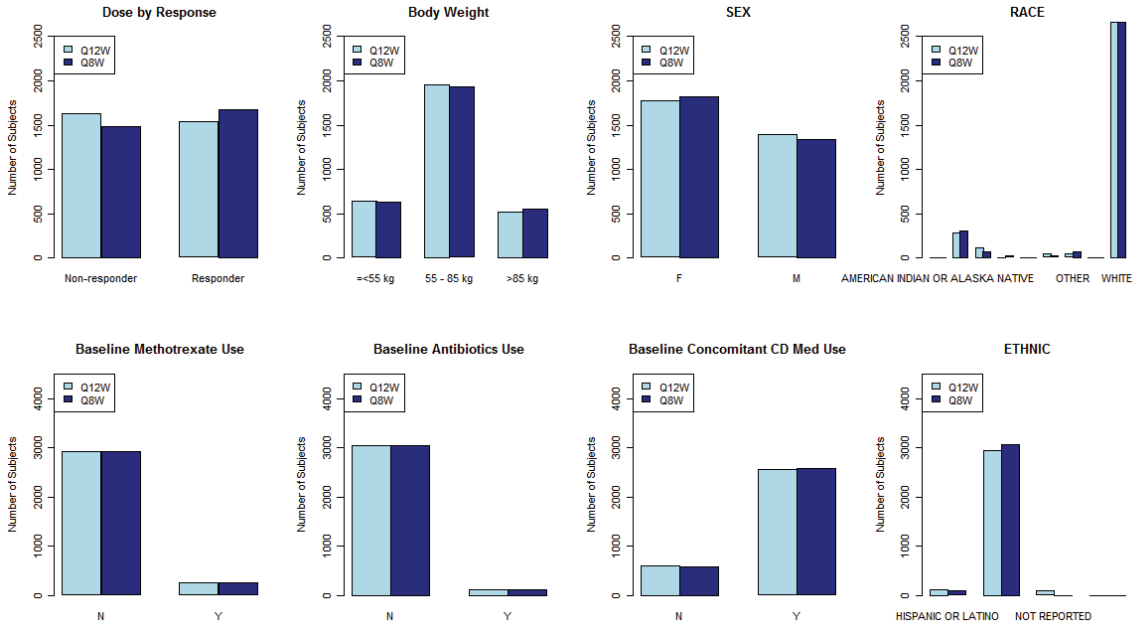


Figure 5. Baseline Risk Factors by Maintenance Dosing Regimen *(Source: Reviewer's analysis)*

(b) (4)

Table 2. Clinical Remission and Clinical Response 16 Weeks after Dose Adjustment*

Adjusted dose	N	Clinical remission	Clinical response
Q12W → Q8W	29	41.4%	55.2%
Q8W → Q8W*	28	32.1%	46.4%

** Subjects at Q8W who met LOR continue to have Q8W and clinical remission and clinical response at 16 weeks after LOR were compared (Source: CNTO1275CRD3003)*

Patients who lost response with Q12W dosing and escalated dose to Q8W dosing showed higher clinical remission rate (55.2%) and clinical response rate (41.4%) 16 weeks after dose adjustment compared to those started with Q8W dosing and continued Q8W dosing upon loss of response (46.4% and 32.1%, respectively). However, it is not possible to tease out if this difference is due to longer treatment on the therapy or the escalated dosing regimen. Data from the Q8W → Q8W arm suggest that additional time on the same dosing regimen also results in substantial proportion of patients becoming responders or remitters. Therefore, the utility of Q12W dosing regimen as a starting dose with an option for dose escalation to Q8W does not appear to be supported by observed data.

1.1.4 Is the labeling statement for drug-drug interaction based on the population PK analysis results?

No. (b) (4)

1.2 Recommendations

The submission is acceptable from a Clinical Pharmacology perspective.

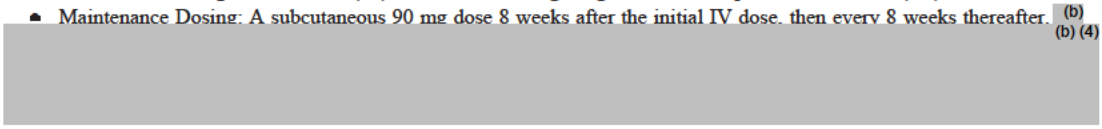
1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

DOSAGE AND ADMINISTRATION

Crohn's Disease

- Initial Dose: A single intravenous (IV) infusion dose using weight-based tiers specified in Table 1 (2.1)
- Maintenance Dosing: A subcutaneous 90 mg dose 8 weeks after the initial IV dose, then every 8 weeks thereafter. (b) (b) (4)



12.3. Pharmacokinetics

Drug-Drug Interactions

Population pharmacokinetic data analyses indicated that the clearance of ustekinumab was not impacted by (b) (4) (b) (4) prior exposure to anti-TNFα agents in patients with (b) (4) Crohn's disease.

2 PERTINENT REGULATORY BACKGROUND

Ustekinumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody to human interleukin (IL)-12/23p40 that binds to human IL-12 and IL-23. It was approved

for the treatment adults (18 years or older) with moderate to severe plaque psoriasis in 2009. The approved SC dosage for the treatment of psoriasis was 45 mg at Week 0 followed by 45 mg Q12W from Week 4 for patients weighing ≤100 kg and 90 mg at Week 0 followed by 90 mg Q12W from Week 4 for patients weighing >100 kg. The current submission is for the treatment of adults with moderate to severe Crohn's Disease and the proposed dosing regimen is 260 mg IV for patients weight ≤55 kg, 390 mg for patients weighing >55 kg to ≤85 kg, and 520 mg for patients weighing >85 kg at Week 0 followed by 90 mg SC Q8W at Week 8. (b) (4) (b) (4) The efficacy and safety for Crohn's Disease was evaluated in two Phase 2 studies (C0379T07, C0743T26) and two Phase 3 induction studies (CNTO1275CRD3001 [CRD3001], CNTO1275CRD3002 [CRD3002]) and a Phase 3 maintenance study (CNTO1275CRD3003 [CRD3003]).

Table 3 Summary of Phase 2 and Phase 3 studies in subjects with CD

Study Number Duration	**Study Population**	**Treatment Groups ad Numbers of Subjects**
Phase 2		
C0379T07 data assessed through W28	Moderately to severely active Crohn's disease despite treatment with conventional therapy (Population 1) or failure to respond to, or loss of response to infliximab (Population 2)	Population 1 (N=104): • Ustekinumab 90 mg SC at W0, 1, 2, 3; placebo SC at W8, 9, 10, 11 (N=25) • Placebo SC at W0, 1, 2, 3; Ustekinumab 90 mg SC at W8, 9, 10, 11 (N=26) • Ustekinumab 4.5 mg/kg IV at W0; placebo IV at W8 (N=26) • Placebo IV at W0; Ustekinumab 4.5 mg/kg IV at W8 (N=27) Population 2 (N=27): • Ustekinumab 90 mg SC at W0, 1, 2, 3 (N=14) • Ustekinumab 4.5 mg/kg IV at W0 (N=13)
C0743T26 36 weeks	Moderately to severely active Crohn's disease; TNF antagonist failure population	Induction phase (N=526): • Placebo IV at W0 (N=132) • Ustekinumab 1 mg/kg IV at W0 (N=131) • Ustekinumab 3 mg/kg IV at W0 (N=132) • Ustekinumab 6 mg/kg IV at W0 (N=131) Maintenance phase (based on clinical response at W6): Subjects in response to ustekinumab IV induction (Randomized subjects; N=145): • Placebo SC at W8 and W16 (N=73) • Ustekinumab 90 mg SC at W8 and W16 (N=72) Nonresponders to ustekinumab IV induction

		(randomized subjects, N=219): • Placebo SC at W8 and W16 (N=110) • Ustekinumab 90 mg SC at W8 and W16 (N=109) Nonrandomized subjects (N=113): • Placebo SC at W8 and W16 (responders to placebo IV induction, N=28) • Ustekinumab 270 mg SC at W8 and 90 mg SC at W16 (nonresponders to placebo IV induction, N=85)
Phase 3		
CNTO1275CRD3001 (induction study) 8 weeks	Moderately to severely active Crohn's disease; TNF antagonist failure population	Single IV induction dose at W0 (N=741 [769 total]) • Placebo (N=247) • Ustekinumab 130 mg (N=245) • Tiered (weight-based ustekinumab doses (N=249)
CNTO1275CRD3002 (induction study) 8 weeks	Moderately to severely active Crohn's disease; Conventional therapy (corticosteroids and/or immunomodulators) failure population	Single IV induction dose at W0 (N=628 [640 total]) • Placebo (N=210) • Ustekinumab 130 mg (N=209) • Tiered (weight-based ustekinumab doses (N=209)
CNTO1275CRD3003(maintenance study) Data through Week 44 (272 weeks total duration when completed)	Subjects from both Phase 3 induction studies could continue into this maintenance study	Subjects in response to ustekinumab induction (Randomized subjects; N=388 [397]) • Placebo SC (N=133) • Ustekinumab 90 mg SC Q12W (N=132) • Ustekinumab 90 mg SC Q8W (N=132) Other population (non-randomized subjects; N=884) • Placebo SC (responders to placebo IV induction, N=123) • Ustekinumab 90 mg SC Q8W (nonresponders to ustekinumab IV induction, N=476) • Ustekinumab 90 mg SC Q12W (nonresponders to placebo IV induction, N=285)

(Source: SCE Table 1, page 10)

The induction dose of IV 130 mg regardless of body weight was compared to the proposed weight-tiered IV dosing in the two Phase 3 induction studies and showed efficacy benefits without safety concerns. The results from the Phase 3 studies are summarized in Table 4 for the induction phase and Table 5 for the maintenance phase.

Table 4. Efficacy Results from Phase 3 Induction Studies (CRD 3001 and CRD3002)

	CRD3001 (TNFα failures)			**CRD3002 (conventional therapy failures)**		
	Placebo (%, N=247)	130 mg STELARA(%, N=245)	~6 mg/kg STELARA (%, N=249)	Placebo (%, N=209)	130 mg STELARA (%, N=209)	~6 mg/kg STELARA (%, N=209)
Clinical response at Week 6	**21.5**	**34.3**	**33.7**	**28.7**	**51.7**	**55.5**
Clinical remission at Week 8	7.3	15.9	20.9	19.6	30.6	40.2
Clinical response at Week 8	20.2	33.5	37.8	32.1	47.4	57.9
70-point response at Week 6	30.4	46.1	43.8	38.8	58.9	64.6
70-point response at Week 3	27.1	38.4	40.6	31.6	49.3	50.7

(Source: SCE Table 11, page 88)

Table 5. Efficacy Results from Phase 3 Maintenance Study (CRD3003)

	Placebo (N=131)	**90 mg STELARA Q8W (N=128)**	**90 mg STELARA Q12W (N=129)**
Clinical Remission	36%	53%	49%
Clinical Response	44%	59%	58%
Corticosteroid-Free Clinical Remission	30%	47%	43%
Sustained Clinical Remission	26%	46%	40%
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)	56% (44/78)
who are Anti-TNFα refractory/intolerant	26% (16/61)	41% (23/56)	39% (22/57)

who failed conventional therapy but not anti-TNFα therapy	44% (31/70)	63% (45/72)	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)	57% (30/53)

(Source: SCE Table 5, page 59)

The sponsor found both Q8W and Q12W dosing regimens efficacious and safe for the maintenance phase without statistically significant differences for primary and secondary endpoints and proposes both without clear distinction between the target beneficiaries.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK Analysis

A population PK model of ustekinumab was developed using PK data obtained from Studies C0743T26, CRD3001, CRD3002, and CRD3003. The analysis was employed to describe the PK characterizes of ustekinumab following IV ad SC administration and to evaluate the influence of covariates on the disposition of ustekinumab in subjects with Crohn's disease. The final population PK model was also to be used to generate ustekinumab exposure predictions to support exposure-response analyses described in section 3.2. The base model was selected based on comparison between different structural models and then the full model was developed with additional covariates that influence ustekinumab PK. The final model was selected based on the maximum NONMEM-based Schwarz Bayesian criterion (SBC) among the top 15 ranked models. Besides statistical significance evaluation, visual predictive checks and other goodness-of-fit plots were used for model selection and to evaluate the predictive performance of the models.

The ustekinumab PK was adequately described by a 2-compartment model and Table 6 summarized the PK parameter estimates of the final model.

Table 6. Parameters Estimates for the Final Population PK Model

Name	Parm	Estimate (ASE/RSE)[a]	Trans. Estimate[b]	Transformed 95% CI	Trans. Units	Effect Magnitude[c]
CL	th2	-1.65(0.0162)	0.191	(0.185,0.197)	L/d	
CL-BWGT	th8	0.481(0.0384)	1.11	(1.03,1.2)	frac*	0.918, 1.09
CL-BALB	th12	-0.972(0.0549)	0.805	(0.723,0.896)	frac*	1.12, 0.927
CL-SEX=M	th19	0.161(0.0164)	1.17	(1.14,1.21)	frac	+17%
CL-RACE=A	th21	0.135(0.0303)	1.14	(1.08,1.21)	frac	+14%
CL-FTNF	th24	0.109(0.0149)	1.11	(1.08,1.15)	frac	+11%
CL-IBCRP	th30	0.0705(0.00542)	1.02	(1.01,1.03)	frac*	0.932, 1.07
CL-IRPT	th36	0.125(0.124)	1.13	(0.889,1.45)	frac	+13%
V2	th1	1.01(0.00852)	2.74	(2.69,2.78)	L	
V2-BWGT	th7	0.402(0.0254)	1.09	(1.04,1.15)	frac*	0.931, 1.07
V2-BALB	th11	-0.208(0.0397)	0.955	(0.883,1.03)	frac*	1.02, 0.984
V2-SEX	th14	0.155(0.0125)	1.17	(1.14,1.2)	frac	+17%
Q	th4	-1.25(0.26)	0.287	(0.173,0.478)	L/d	
Q-BWGT	th10	0.793(0.289)	1.19	(0.677,2.1)	frac*	0.868, 1.15
V3	th3	0.63(0.064)	1.88	(1.66,2.13)	L	
V3-BWGT	th9	0.705(0.0932)	1.17	(0.975,1.41)	frac*	0.882, 1.13
KA	th5	-1.71(0.0498)	0.181	(0.164,0.2)	(1/d)	
F1	th6	1.28(0.0687)	0.783	(0.759,0.805)	frac	
Var(CL)	Ω(CL)	0.0849(0.00379)	29.1	(27.9,30.4)	%CV	
Covar(CL,V2)	Ω(CL, V2)	0.0218(0.0022)	0.0218	(0.0175,0.0261)	--	
Var(V2)	Ω(V2)	0.0215(0.00191)	14.7	(13.4,15.9)	%CV	
Covar(CL,V3)	Ω(CL, V3)	-0.0496(0.0114)	-0.0496	(-0.072,-0.0272)	--	
Var(V3)	Ω(V3)	0.104(0.0564)	32.2	(15.1,49.4)	%CV	
Var(Q)	Ω(Q)	0.571(0.367)	75.6	(27.9,123)	%CV	
Var(ka)	Ω(Ka)	0.52(0.103)	72.1	(58.1,86.1)	%CV	
Var(F1)	Ω(F1)	1.05(0.155)	1.02	(0.874,1.17)	SD logit	
Var(eps1)	σ^2(Prop)	0.0287(0.000861)	16.9	(16.4,17.4)	%CV	
Var(eps2)	σ^2(Add)	0.00558(0.00055)	0.0747	(0.0675,0.0819)	SD	

Parm. = Parameter; ASE = Approximate Standard Error; RSE = Relative Standard Error; Trans. = Transformed; frac = fraction; frac* = fractional change displayed in Transformed Estimate column computed at a 25% increase in the covariate (see below); d = day; L = liter; %CV = approximate percent coefficient of variation; SD = standard deviation; M = Males; A = Asian

[a] The ASE can be interpreted as an approximate RSE for parameters which are restricted to be positive (eg, CL).

[b] Transformed estimate is the estimate translated to the standard pharmacokinetic scale, and takes units described in Trans. Unit column. For discrete covariate effects, the fractional change in the pharmacokinetic parameter is reported – ie, $exp(\theta \cdot X)$, where X is the covariate value and $X = 1$. For continuous covariate effects, the reported estimate is based on a 25% increase in the covariate – ie, $exp(\theta \cdot [\ln(1.25 \cdot X) - \ln X_{median}]) = (1.25 \cdot X/X_{median})^{\theta} = (1.25)^{\theta}$.

[c] For continuous covariates – indicated by frac* in the Trans. Units column – the effect magnitude is computed at the 25th and 75th percentile of the observed covariate distribution – ie, $(X_{25th\%-tile}/X_{median})^{\theta}$ and $(X_{75th\%-tile}/X_{median})^{\theta}$, respectively. For discrete covariates, the Effect Magnitude value reported is the percent change – ie, $100 \times (exp(\theta \cdot X) - 1)$.

(Source: Sponsor's Population PK Report, Table S1, page 13)

The typical value [95% CI] of CL for a subjects weighing 70 kg was 0.191 [0.185-0.197] L/day, V2 was 2.74 [2.69-2.78]. The inter-individual variability was 29.1% for CL and 14.7% for V2. The bioavailability was estimated to be 78.3% and the median terminal half-life was approximately 19 days. Among the evaluated covariates, body weight was significant on CL, V2, V3 and Q. In addition, sex and race were significant covariates on CL and TNF antagonist failure status, immunogenicity; CRP levels, sex, and race were found to be significant covariates on V (Figure 6).

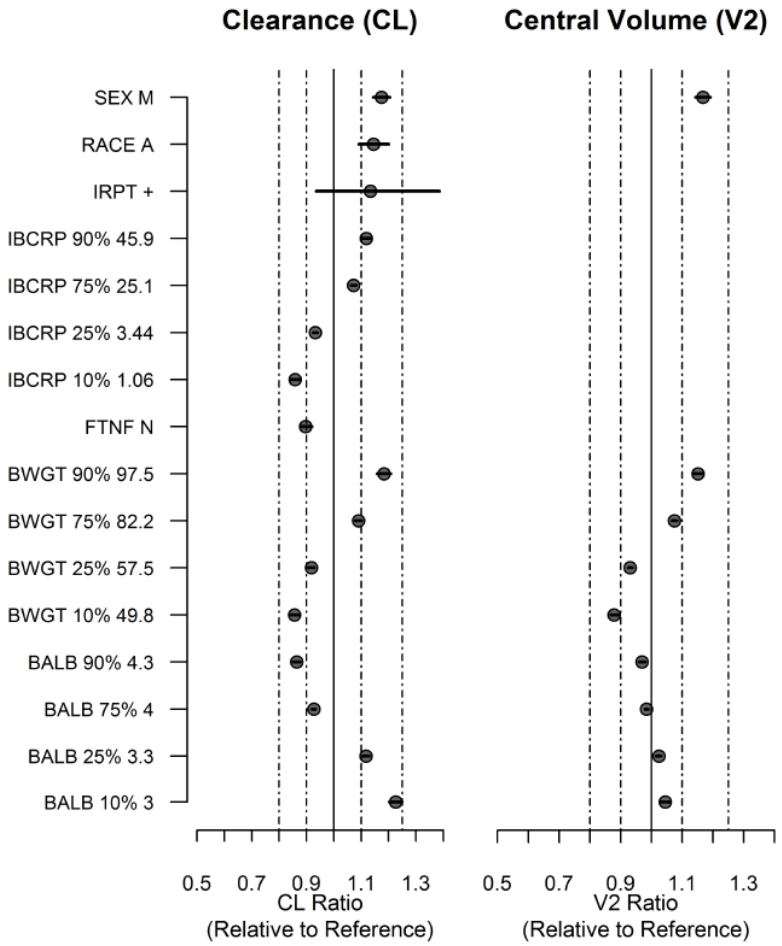


Figure 6. Effects of Covariates on CL and V2 using the Final Population PK Model
(Source: Sponsor's Population PK Report, Figure 7 on page 51)

Although the effect size of the body weight on ustekinumab PK was not large, the body weight was a significant covariate on CL which justified the proposed weight-tiered dosing regimen for induction.

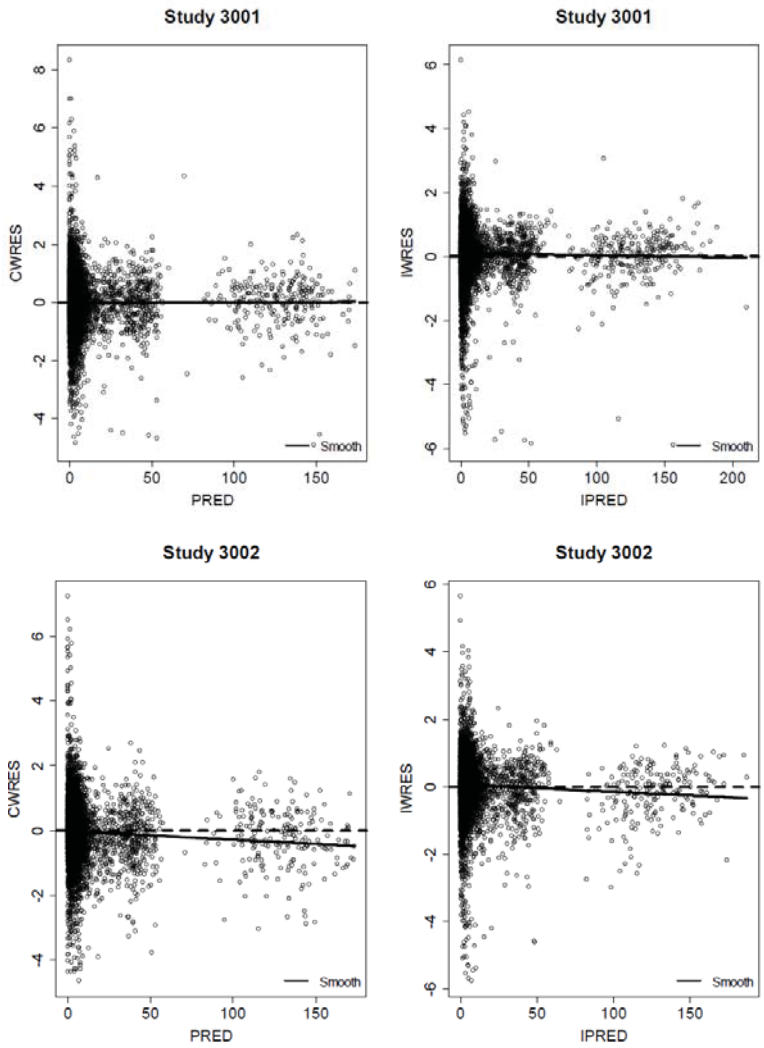


Figure 7. Diagnostics Plots for Final Model (CWRES: Conditional Weighted Residuals, IWRES: Individual Weighted Residuals, PRED: Predicted for Typical Patients, IPRED: Predicted for Individual Patients) *(Source: Sponsor's Population PK Report, page 103-104)*

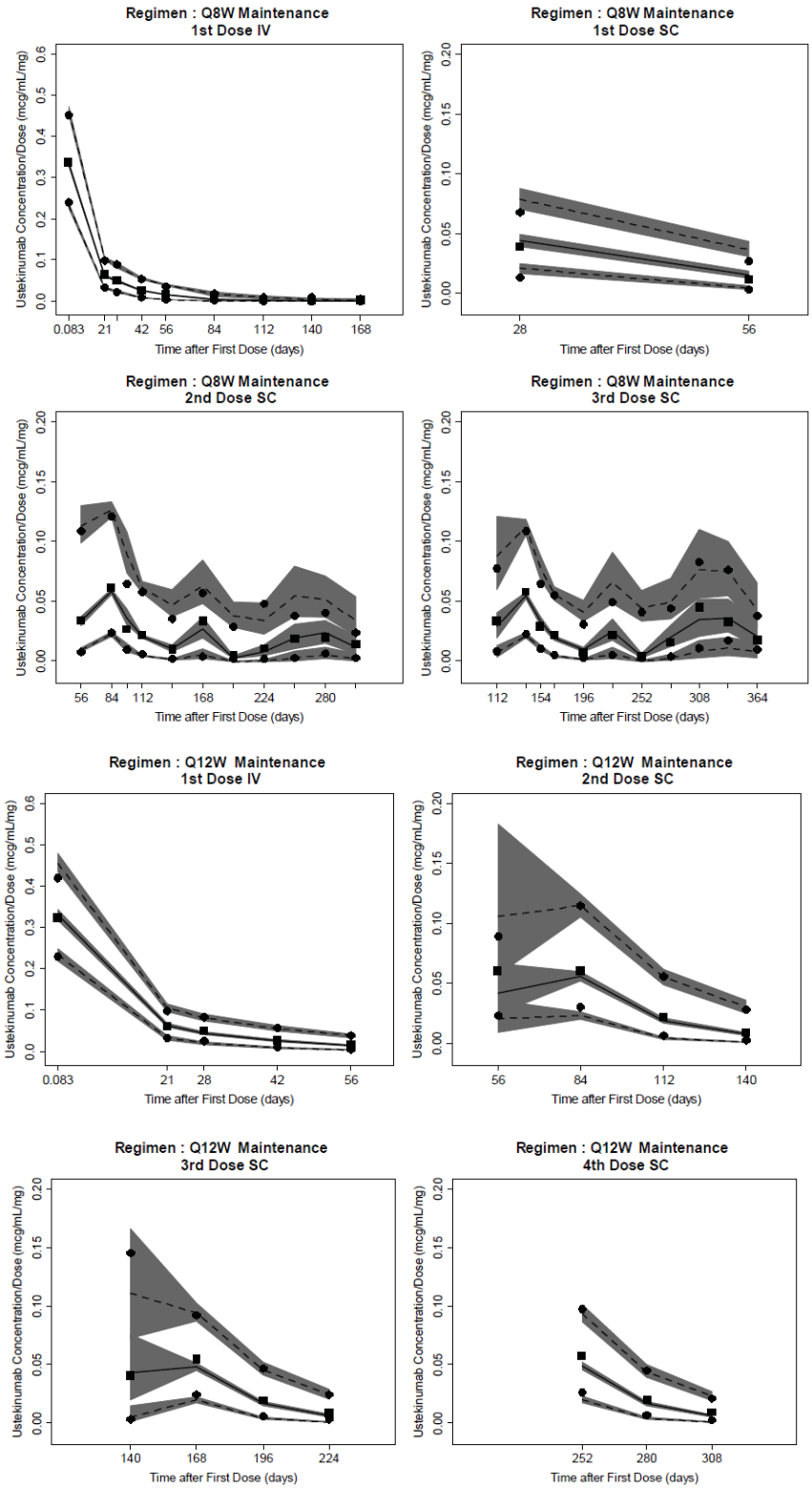


Figure 8. Visual Predictive Checks for the Final Model *(Source: Sponsor's Population PK Report, Figure 8 on 52)*

Reviewer's comments:

The final model appears to adequately describe the observed PK data. The plots for goodness-of-fit and visual predictive check indicate that the predicted values with the final model could be reasonable. (b) (4)

During the model development, the sponsor reduced the full model to the final model by multiple steps of removal of covariates due to an estimation failure of the full model with an approximation algorithm for covariate analysis (WAM). Even after removal of a subset of covariates, the model still did not converge and consequently, the effect of some covariates was set to 0 in the final model for fitting purpose, which means the effect of these covariates was forced to "not be influential" in estimation step. Those covariates include concomitant medications such as methotrexate (MTX), azathioprine (AZA), 6-mercaptopurine (6-MP), and oral corticosteroids. Furthermore, the data for concomitant medications were not reported as time-varying components so the effect of concomitant medication could not adequately evaluated using the covariate analysis. Thus, PK parameters could not be adequately estimated for those patients with concomitant medication. (b) (4)

In the final model, body weight, baseline albumin, SEX, failure to previous TNFα therapy, baseline CRP, baseline platelet counts, baseline fecal calprotectin were included as covariate that affect ustekinumab clearance. Among those covariates, body weight and baseline albumin were predicted to have a meaningful effect on ustekinumab PK.

3.2 Exposure-Response Analysis

The sponsor evaluated the exposure-response relationship between ustekinumab concentration and Clinical Response at Week 6 (Figure 9). The exposure-response relationship between ustekinumab concentration and clinical remission at Week 44 (Week 52 referenced to Week 0 of induction phase) was also evaluated (Figure 10). Ustekinumab concentrations were predicted with the final population PK model for both exposure-response analyses. For the induction phase, a total of 23 subjects were excluded (1.2%, 23 out of 1932) due to missing PK or necessary information for PK predictions. For the maintenance phase, a total of 9 subjects were excluded (2.3%, 9 out of 396 subjects) for the same reasons. Subjects who dropped out early or who received a dose adjustment were regarded as treatment failure and the most recent trough concentration prior to dropout or dose adjustment was used as the exposure variable for these patients.

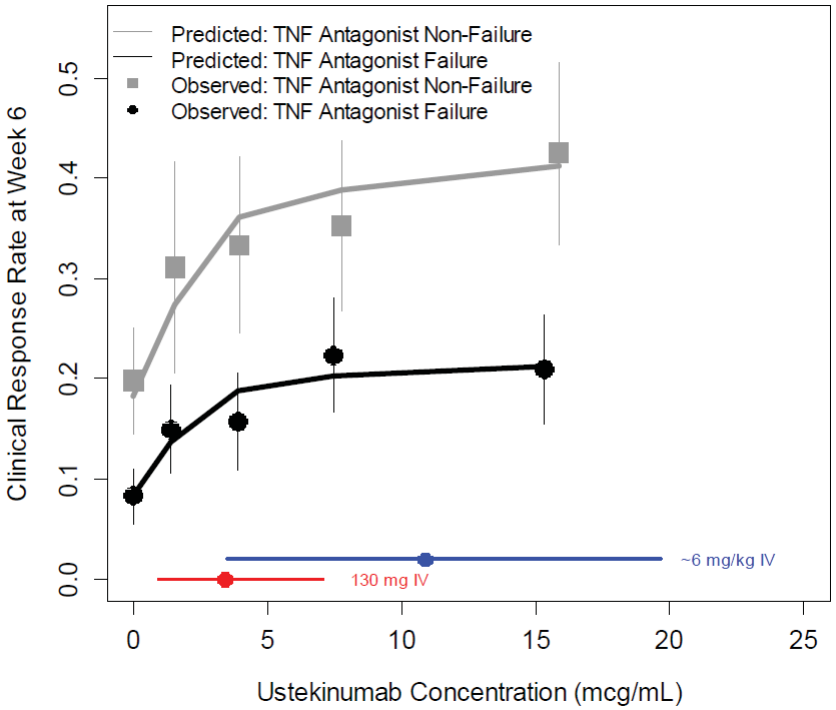


Figure 9. Exposure-Response Relationship between Ustekinumab Concentration and Clinical Response at Week 6 (ustekinumab concentrations were predicted with the final population PK model) *(Source: Sponsor's Exposure-Response Analysis Report, Figure 2, page 25)*

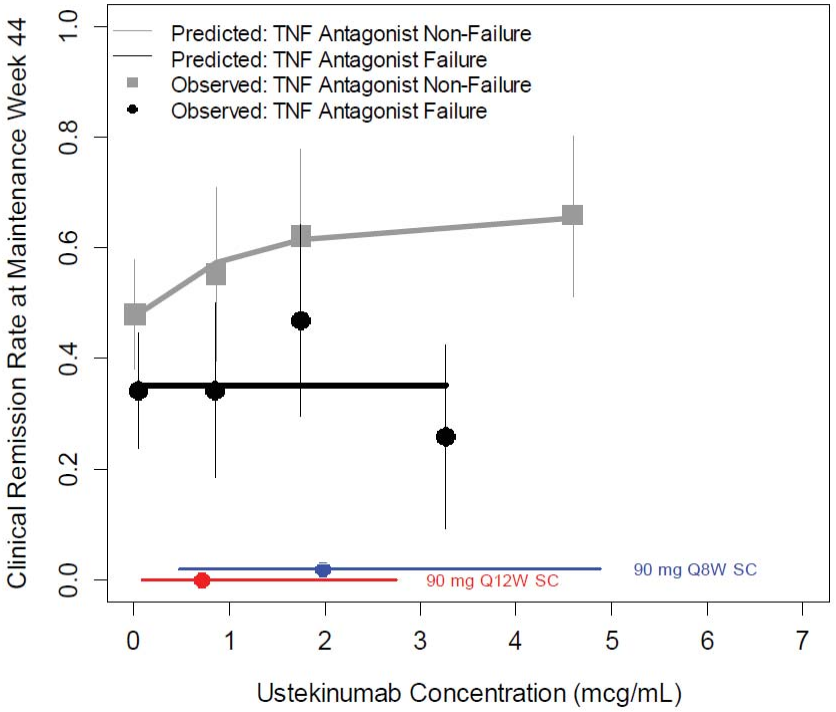


Figure 10. Exposure-Response for Clinical Remission at Week 44 (Week 52 referenced to Week 0 in induction phase, ustekinumab concentrations were predicted with the final population PK model)
(Source: Sponsor's Exposure-Response Analysis Report, Figure 3, page 29)

As shown in Figure 9, an exposure-response relationship between the predicted ustekinumab concentrations and clinical response at Week 6 exists with the studied induction dosing regimens, and the relationship appears to be different by anti-TNFα therapy status. The relationship between ustekinumab concentration and clinical remission at Week 44 appears to be flat in patients who failed to previous anti-TNFα therapy and shallow in patients who did not (Figure 10).

Reviewer's comments:

Although the exposure-response relationships between patients who failed to previous anti-TNFα therapy and those who did not are distinctively different, this difference does not lead to a need for different dose by the anti-TNFα therapy status.

For the exposure-response in the induction phase, similar levels of ustekinumab concentration appear to be needed to achieve the maximal drug effect for both TNFα antagonist failure and TNFα antagonist non-failure populations.

For exposure-response in the maintenance phase, the predicted ustekinumab concentrations were higher with Q8W dosing regimen than those with Q12W dosing regimen, while the relationship between exposure and response for TNFα antagonist non-failure patients was shallow. This is consistent with the modestly higher numerical benefit observed with Q8W regimen compared to the Q12W dosing regimen. However, the lack of exposure-response relationship in TNFα antagonist failure population indicates that ustekinumab was not different from the placebo which is not consistent with the observed results from the maintenance phase clinical study 3003. It is worth noting that the exposure-response analysis in the maintenance phase was not utilized for any regulatory decision making in this review and therefore no further discussion on the exposure-response analysis for the maintenance phase is included hereafter.

3.3 Subgroup Analysis for Effect of Weight

From the reviewer's analysis, the efficacy rates were found to be lower in patients weighing ≤55 kg with 260 mg dose compared to other weight groups of patients who received 390 mg and 520 mg for induction. The response and remission rates following placebo in patients weighing ≤55 kg were also lower than those in patients weighing >55 kg. To evaluate the effect of lower exposures of ustekinumab in patients with lower body weight, a subgroup analysis for the efficacy during the maintenance by body weight would be important. Thus an information request (IR) was sent to the sponsor.

According to the sponsor's response to the IR, the lower induction rate in this group of patients do not seem to have an effect on the efficacy in the maintenance with continuous dosing of ustekinumab. The clinical remission rate at Week 44 (Week 52 referenced to Week 0 of induction phase) was higher than that in other weight groups of patients (Table 7 & Table 8).

Table 7. Summary of Dose and Efficacy in Patients Who Failed to Prior TNFα Antagonists by Body Weight Group

Induction Dose	Body Weight	Subjects randomized for induction (N)	Week 6 Responders during induction (N[%])	Subjects randomized for maintenance (N)		Week 44 Remitters (N[%])	
				Q8W	Q12W	Q8W	Q12W
130 mg	≤55 kg	54	19 (35.3%)	4	6	1 (25%)	5 (83.3%)
130 mg	55-85 kg	157	58 (37%)	18	16	9 (50%)	8 (50%)
130 mg	>85 kg	34	7 (20.6%)	2	4	1 (50%)	3 (75%)
260 mg	≤55 kg	57	17 (29.8%)	7	5	4 (57.1%)	3 (60%)
390 mg	55-85 kg	147	52 (35.4%)	20	20	7 (35%)	7 (35%)
520 mg	>85 kg	45	15 (33.3%)	6	5	4 (66.7%)	1 (20%)

(Source: Sponsor's response to July 21 2016 FDA Discipline Review Letter Information Requests, dated to July 29 2016)

Table 8. Summary of Dose and Efficacy in Patients Who Failed to Conventional Therapy (TNFα Antagonist Non-Failure) by Body Weight Group

Induction Dose	Body Weight	Subjects randomized for induction (N)	Week 6 Responders during induction (N[%])	Subjects randomized for maintenance (N)		Week 44 Remitters (N[%])	
				Q8W	Q12W	Q8W	Q12W
130 mg	≤55 kg	37	26 (70.3%)	9	8	7 (77.8%)	7 (87.5%)
130 mg	55-85 kg	121	58 (47.9%)	18	17	14 (77.8%)	10 (58.8%)
130 mg	>85 kg	51	24 (47.1%)	8	7	3 (37.5%)	5 (71.4%)
260 mg	≤55 kg	41	15 (36.6%)	7	7	6 (85.7%)	5 (71.4%)
390 mg	55-85 kg	125	82 (65.6%)	25	29	16 (64%)	20 (69%)

520 mg	>85 kg	43	19 (44.2%)	5	4	3 (60%)	3 (75%)

(Source: Sponsor's response to July 21 2016 FDA Discipline Review Letter Information Requests, dated to July 29 2016)

4 REVIEWER'S ANALYSIS

4.1 Introduction

The sponsor's analyses for exposure-response relationships for both induction phase and maintenance phase focused on the comparison of patients with previous anti-TNFα failure and those without it. The effect of weight-tiered dosing regimen on induction or the effect of dose frequency on maintenance could not be evaluated from the sponsor's analyses. The reviewer questioned the validity of the weight-tiered dosing scheme for induction phase since the effect of body weight on ustekinumab was within ±20% for patients with Crohn's Disease.

4.2 Objectives

Analysis objectives are:

1. To evaluate the effect of weight-tiered dosing on ustekinumab exposure and clinical response during the induction.
2. To evaluate the effect of any baseline risk factors on efficacy with Q8W or Q12W maintenance dosing regimen.

4.3 Methods

4.3.1 Data sets

Data sets used in the analysis are summarized in **Table 9**.

Table 9. Analysis Data Sets

Study Number	Name	Link to EDR
Population PK Analysis		\\CDSESUB1\evsprod\BLA761044\0003\m5\datasets\pop-pk\analysis\legacy\datasets
Exposure-Response Analysis	res6_rem8.xpt Rm44data.xpt	\\CDSESUB1\evsprod\BLA761044\0004\m5\datasets\exposure-response\analysis\legacy\datasets
cnto1275crd3001	Adef.xpt Adsl.xpt Adcdai.xpt	\\CDSESUB1\evsprod\BLA761044\0000\m5\datasets\cnto1275crd3001\analysis\adam\datasets
cnto1275crd3002	Adef.xpt Adsl.xpt	\\CDSESUB1\evsprod\BLA761044\0000\m5\datasets\cnto1275crd3002\analysis\adam\datasets

	Adcdai.xpt	
cnto1275crd3003	Adef.xpt Adsl.xpt Adcdai.xpt	\\CDSESUB1\evsprod\BLA761044\0000\m5\datasets\cnto1275crd3003\analysis\adam\datasets

4.3.2 Software

Modeling and simulation with the sponsor's population PK model were performed with NONMEM (version 7.3). The graphical and statistical analyses were performed with R (version 13.1).

4.3.3 Subgroup Analysis for the Effect of Body Weight on Efficacy in Induction Phase

The sponsor's analysis in the original submission compared ustekinumab concentrations and efficacy between 130 mg fixed dosing and weight-tired dosing regimen (~6 mg/kg) and did not evaluate the effect weight-tiered doses on them. Thus the reviewer performed supplementary analysis to evaluate if the weight-tiered doses are adequate by comparing ustekinumab concentrations and efficacy during the induction phase by body weight group. As shown in Figure 1, the observed ustekinumab concentrations at Week 3 and Week 6 following 260 mg in patients weighing ≤55 kg appear to be lower than those in other groups of patients who received higher doses. Thus, the clinical response at Week 6 and the clinical remission at Week 8 were also evaluated to investigate the potential effect of the lower exposure on the efficacy.

Placebo-adjusted clinical remission rate at Week 8 in patients with TNF non-failure was 8.1% following 260 mg in patients weighing ≤55 kg while 23.7% following 390 mg in those weighing 55-85 kg and 17.1% following 520 mg in those weighing >85 kg (Figure 3 (b)). However, the placebo-adjusted remission rate at Week 8 was higher (17.4%) following 130 mg in patients weighing ≤55 kg (Figure 3 (d)), although the exposures following 130 mg in patients weighing ≤ 55 kg were lower than the exposures in patients weighing ≤55 kg who received 260 mg. Placebo-adjusted clinical remission rate at Week 8 in patients with TNF failure, however, was 18.4% following 260 mg in patients weighing ≤55 kg while 13.4% following 390 mg in those weighing 55-85 kg and 16.9% following 520 mg in those weighing >85 kg (Figure 2 (b)).

Difference in disease characteristics between patients who had failed to TNFα therapy and those who had not failed to TNFα therapy might have had an impact on the different response to the new treatment with ustekinumab, and thus further analysis might be useful for an optimal dosing strategy. Since these observations are only for the induction phase, an evaluation of the effect of these lower exposures on the maintenance of the drug effect would be more relevant. Thus, an information request was sent out to the sponsor for additional analysis to evaluate the potential effect of lower exposure on the efficacy, especially on the maintenance of the drug effect (Discipline Review Information Request dated to July 21 201).

4.3.4 Baseline Risk Assessment for Clinical Remission at Week 44

A potential effect of baseline risk factors on response status was evaluated (Figure 4). Visual assessment clearly showed that there are no baseline risk factors associated with response status for clinical remission at Week 44 (Week 52 referenced to Week 0 in induction). Whether the patients were adequately randomized upon initiation of the maintenance was also confirmed by a visual inspection of baseline disease characteristics by dose group (Figure 5). It does not appear that any baseline disease characteristics might have played a role as a confounder.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
BLA761044_ER_Induction.R BLA761044_ER_Maintenance.R BLA761044_CDAI.R BLA761044_pop PK.R		\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ustekinumab_BLA761044_JEL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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JEE E LEE
08/24/2016

NITIN MEHROTRA
08/24/2016