Report on the Deliberation Results

February 17, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Stelara Intravenous Infusion 130 mg
	Stelara Subcutaneous Injection 45 mg Syringe
Non-proprietary Name	Ustekinumab (Genetical Recombination) (JAN*)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 30, 2016

Results of Deliberation

In its meeting held on February 9, 2017, the First Committee on New Drugs concluded that a marketing application for Stelara Intravenous Infusion 130 mg and a partial change approval application for Stelara Subcutaneous Injection 45 mg Syringe may be approved, and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

Stelara Intravenous Infusion 130 mg is classified as a biological product, and the drug product is classified as a powerful drug. The re-examination period for Stelara Intravenous Infusion 130 mg and Stelara Subcutaneous Injection 45 mg Syringe is 6 years.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

January 27, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical products submitted for marketing approval or partial change approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Stelara Intravenous Infusion 130 mg Stelara Subcutaneous Injection 45 mg Syringe
Non-proprietary Name	Ustekinumab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 30, 2016

Dosage Form/Strength

1. Stelara Intravenous Infusion 130 mg:

A solution for infusion in a vial. Each vial contains 130 mg of Ustekinumab (Genetical Recombination).

2. Stelara Subcutaneous Injection 45 mg Syringe:

A solution for injection in a prefilled syringe. Each prefilled syringe contains 45 mg of Ustekinumab (Genetical Recombination).

Application Classification

1. Stelara Intravenous Infusion 130 mg:

Prescription drug, (3) Drug with a new route of administration

2. Stelara Subcutaneous Injection 45 mg Syringe:

Prescription drug, (4) Drug with a new indication and (6) Drug with a new dosage

Items Warranting Special Mention	None
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the products have efficacy in the treatment of patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy, and that the products have acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the products may be approved for the indications and dosage and administration shown below, with the following condition.

Indications

1. Stelara Intravenous Infusion 130 mg:

Induction therapy for moderately to severely active Crohn's disease (only in patients who have had an inadequate response to conventional therapy)

2. Stelara Subcutaneous Injection 45 mg Syringe:

Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:

Psoriasis vulgaris and psoriatic arthritis

Maintenance therapy for moderately to severely active Crohn's disease (only in patients who have had an inadequate response to conventional therapy)

(Underline denotes additions.)

Dosage and Administration

1. Stelara Intravenous Infusion 130 mg:

The usual adult initial dosage of Ustekinumab (Genetical Recombination), infused intravenously as a single dose (induction therapy):

Body weight	Dose
≤55 kg	260 mg
>55 kg and ≤85 kg	390 mg
>85 kg	520 mg

2. Stelara Subcutaneous Injection 45 mg Syringe:

Psoriasis vulgaris and psoriatic arthritis

The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter. If the effect is insufficient, a dose of 90 mg may be used.

Crohn's disease

The usual adult maintenance dosage is a subcutaneous 90 mg dose of Ustekinumab (Genetical Recombination) administered 8 weeks after the intravenous infusion induction dose, then every 12 weeks thereafter. The dosing interval may be shortened to every 8 weeks in patients who have lost response.

(Underline denotes additions.)

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

December 9, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Products Submitted for Approval

Brand Name	Stelara Intravenous Infusion 130 mg
	Stelara Subcutaneous Injection 45 mg Syringe
Non-proprietary Name	Ustekinumab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 30, 2016

Dosage Form/Strength

1. Stelara Intravenous Infusion 130 mg:

A solution for infusion in a vial. Each vial contains 130 mg of Ustekinumab (Genetical Recombination).

2. Stelara Subcutaneous Injection 45 mg Syringe:

A solution for injection in a prefilled syringe. Each prefilled syringe contains 45 mg of Ustekinumab (Genetical Recombination).

Proposed Indications

1. Stelara Intravenous Infusion 130 mg:

Induction of remission in patients with moderately to severely active Crohn's disease

2. Stelara Subcutaneous Injection 45 mg Syringe:

Treatment of the following diseases in patients who have had an inadequate response to conventional therapy: Psoriasis vulgaris and psoriatic arthritis

<u>Maintenance therapy after induction therapy with ustekinumab intravenous infusion in patients with moderately to severely active Crohn's disease</u>

(Underline denotes additions.)

Proposed Dosage and Administration

1. Stelara Intravenous Infusion 130 mg:
   The usual adult initial dosage of Ustekinumab (Genetical Recombination), infused intravenously as a single dose:

Body weight	Dose
≤55 kg	260 mg
>55 kg and ≤85 kg	390 mg
>85 kg	520 mg

2. Stelara Subcutaneous Injection 45 mg Syringe:

Psoriasis

The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter. If the effect is insufficient, a dose of 90 mg may be used.

Crohn's disease

The usual adult maintenance dosage is a subcutaneous 90 mg dose of Ustekinumab (Genetical Recombination) administered 8 weeks after the initial intravenous infusion induction dose, then every 8 weeks thereafter.
Dosing every 12 weeks after the first subcutaneous dose may be acceptable for patients with a lower inflammatory burden. Patients who inadequately respond to 90 mg subcutaneous dosing every 12 weeks may be dosed every 8 weeks.

(Underline denotes additions.)

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List of Abbreviations

Study 3001	Global phase III study (CTD 5.3.5.1.1, Study ID CRD3001)
Study 3002	Global phase III study (CTD 5.3.5.1.2, Study ID CRD3002)
Study 3003	Global phase III study (CTD 5.3.5.1.3-1, Study ID CRD3003)
5-ASA	5-aminosalicylate acid
6 mg/kg group	Subjects who received a single intravenous dose of ustekinumab as specified below: body weight ≤55 kg, 260 mg; body weight >55 kg and ≤85 kg, 390 mg; body weight >85 kg, 520 mg
6-MP	6-mercaptopurine
90 mg/q12w group	Subjects who received 90 mg ustekinumab subcutaneously every 12 weeks
90 mg/q8w group	Subjects who received 90 mg ustekinumab subcutaneously every 8 weeks
AUC	Area under the curve
AZA	Azathioprine
Study C0743T26	Foreign phase II study (CTD 5.3.5.1.5, Study ID C0743T26)
Study C30379T07	Foreign phase II study (CTD 5.3.5.1.4, Study ID C30379T07)
CD	Crohn's disease
CDAI	Crohn's disease activity index
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
cIEF	Capillary isoelectric focusing
CR	Clinical response
CRP	C-reactive protein
CTD	Common Technical Document
[redacted]	[redacted]
GCP	Good clinical practice
Ht	Hematocrit
IL	Interleukin
IV	Intravenous injection
LOCF	Last observation carried forward
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MTX	Methotrexate
RH	Relative humidity
SC	Subcutaneous injection
TNF	Tumor necrosis factor
Pre-filled syringe drug product	Stelara Subcutaneous Injection 45 mg Syringe (Approval No. 22300AMX00422000)
Vialed drug product	Stelara Intravenous Infusion 130 mg
PMDA	Pharmaceuticals and Medical Devices Agency
Ustekinumab	Ustekinumab (Genetical Recombination)

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Crohn's disease (CD) is a granulomatous inflammatory bowel disease. The earliest findings are multiple aphthae and aphtha-like ulcers present in the gastrointestinal mucosa, which develop into longitudinal ulcers, cobblestone appearances, and lesions with fibrosis. Any part of the gastrointestinal tract may be affected discontinuously and transmurally from the mouth to the anus. Patients with CD present with gastrointestinal symptoms such as diarrhoea, abdominal pain, bloody stool/melena, anal lesions, and external fistulae as well as systemic symptoms such as fever, malaise, and anaemia, and experience relapses and recurrences.

In Japan, in accordance with 2014 revised version of the Diagnostic Criteria/Treatment Guidelines for ulcerative colitis and Crohn's disease (Health and Labour Sciences Research Grant, Rare/Intractable Disease Project, "Research on intractable inflammatory bowel disease" [Leader, Suzuki], *2014 Research Report*. 2015;19-22) etc., treatment (nutritional therapy, drug therapy, surgery, etc.) is selected according to the severity of the disease, etc. Mesalazine preparations are used for relatively mild active CD. For mildly to moderately active CD, corticosteroids are used, and if dose reduction/withdrawal of corticosteroids is difficult, immunomodulators are used. For patients with moderately to severely active CD who have had an inadequate response to conventional therapy with mesalazine or corticosteroids, etc., the use of biologics (anti-TNF agents) is considered. However, as there are patients who respond inadequately to anti-TNF therapy, etc., there is a need for a new treatment option.

Ustekinumab (Genetical Recombination) (hereinafter referred to as ustekinumab) is a human immunoglobulin G1κ monoclonal antibody against human interleukin (IL)-12/23 p40. CD patients have increased secretion of IL-12 and IL-23 by intestinal antigen-presenting cells (*Gastroenterology*. 1997; 112: 1169-1178, *J Leukoc Biol*. 2011; 89: 597-606). Treatment with anti-IL-12/23 p40 antibody was effective in a mouse model of colitis (*J. Immunol*. 1998; 161: 3143-3149, *J Exp Med*. 2006; 203: 2473-2483, etc.). Thus, the applicant undertook the development of ustekinumab for the treatment of CD and has now filed a marketing application for an intravenous formulation of ustekinumab (the vial drug product) and a partial change approval application for a subcutaneous formulation of ustekinumab (the pre-filled syringe drug product), based on the claim that clinical studies etc. have confirmed the efficacy and safety of ustekinumab.

In Japan, the subcutaneous formulation of ustekinumab was approved for the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy in January 2011.

Outside Japan, the subcutaneous formulation of ustekinumab was first approved in Canada in December 2008 for the indication of psoriasis. As of March 2016, it has been approved in ≥80 countries including the US and EU. As to the indication of CD, the intravenous and subcutaneous formulations of ustekinumab have been approved in the US in September 2016 and in the EU in November 2016 for the treatment of patients with moderately to severely active CD who have had an inadequate response to conventional therapy.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

This section describes the intravenous formulation of ustekinumab (the vial drug product) submitted for marketing approval as a drug with a new route of administration.

2.1 Drug substance

Since the drug substance of the intravenous formulation (the vial drug product) is the same as that of the approved subcutaneous formulation (the pre-filled syringe drug product), no new drug substance quality data have been submitted for the current application.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The intravenous formulation (the vial drug product) of ustekinumab is available as a 130 mg/26 mL solution in a vial. It contains the following excipients: sucrose, L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, L-methionine, EDTA disodium salt dihydrate, and water for injection.

2.2.2 Manufacturing process

The intravenous formulation (the vial drug product) is manufactured through a process comprised of thawing of the drug substance, mixing, [redacted], [redacted], sterile filtration, filling, secondary packaging, and testing/storage. [redacted] have been defined as critical steps.

Validation of the commercial-scale manufacturing process has been performed.

2.2.3 Manufacturing process development

Global phase III studies (CRD3001, CRD3002, CRD3003) were initiated with another 5 mg/mL formulation different from the intravenous formulation (the vial drug product). However, as [redacted] was found in some batches of this 5 mg/mL formulation, the drug solution of the approved subcutaneous formulation (the pre-filled syringe drug product) was filled in vials (FVP, 90 mg/mL) and used as an alternative. Then, stability studies [see Section 2.2.5] and a foreign phase I study (NAP1002) [see Section 6.2.1] were conducted with an optimized 5 mg/mL formulation, which was chosen as the to-be-marketed intravenous formulation (the vial drug product).

2.2.4 Control of drug product

The proposed specifications for the intravenous formulation (the vial drug product) consist of quantity, appearance, identification (dot blotting), osmolarity, pH, purity (opacity, CE-SDS [non-reducing and reducing], [redacted]), charge heterogeneity (cIEF), bacterial endotoxins, extractable volume, foreign insoluble matter, translucent particles ([redacted]), insoluble particulate matter, sterility, potency (a cell-based assay), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

The primary stability studies on the intravenous formulation (the vial drug product) are shown in Table 1.

Table 1. Overview of primary stability studies on drug product

Study	No. of batches	Storage conditions	Testing period	Storage package
Long-term	**5**	**5 ± 3°C**	**24 months[a)]**	**Glass vial with a butyl rubber stopper**
Accelerated	**5**	**25 ± 2°C /60 ± 5%RH**	**[redacted] months**	
Stress	**8**	**[redacted]°C /[redacted]%RH**	**[redacted] months**	
Photostability	**1**	**[redacted]°C, an overall illumination of 1.2 million lux·h and an integrated near ultraviolet energy of 200 W·h/m^2**		**Glass vial with a butyl rubber stopper (primary packaging) and a carton (secondary packaging)**

a) The stability study is ongoing up to [redacted] months.

At the long-term condition, CE-SDS (reducing) [redacted] (purity), the cIEF main peak ([redacted]), and quantity tended to decrease over time and [redacted] tended to increase over time, but there were no significant changes in other attributes tested throughout the testing period.

At the accelerated condition, a decrease in [redacted] and an increase in [redacted] were observed.

At the stress condition, in addition to the changes observed at the accelerated condition, decreases in CE-SDS (reducing) [redacted] (purity), cIEF [redacted] and main peak ([redacted]), and potency were observed.

The photostability data showed that the vial drug product (primary packaged) is photosensitive.

Based on the above, a shelf-life of 24 months was proposed for the intravenous formulation (the vial drug product) when stored in a glass vial with a butyl rubber stopper, protected from light, at 2°C to 8°C.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations etc., PMDA concluded that the quality of the intravenous formulation (the vial drug product) is adequately controlled.

2.R.1 Novel excipient

L-histidine monohydrochloride monohydrate is used in the intravenous formulation (the vial drug product).

2.R.1.1 Specification and stability

L-histidine monohydrochloride monohydrate conforms to the Japanese Pharmacopoeia, and PMDA concluded that there were no problems with the specification and stability.

2.R.1.2 Safety

Based on the submitted data, PMDA concluded that there were no safety issues with L-histidine monohydrochloride monohydrate at the level used in the drug product.

Based on the above, PMDA concluded that there were no particular problems with the use of L-histidine monohydrochloride monohydrate in the intravenous formulation (the vial drug product).

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

No new non-clinical pharmacology data have been submitted for the current application since ustekinumab neutralizes IL-12 and IL-23 from humans and some species of monkeys only and does not neutralize IL-12 or IL-23 from rodents, which are used as animal models of inflammatory bowel disease. The pharmacological effects of ustekinumab (its binding to and neutralization of IL-12 and IL-23, etc.) have already been evaluated during the review of the initial application (see "Review Report for Stelara Subcutaneous Injection 45 mg Syringe" [November 10, 2010]).

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Data on the non-clinical pharmacokinetics of ustekinumab following intravenous and subcutaneous administration have already been submitted and evaluated for the initial application (see "Review Report for Stelara Subcutaneous Injection 45 mg Syringe" [November 10, 2010]).

5. Toxicity and Outline of the Review Conducted by PMDA

The data from intravenous and subcutaneous toxicity studies of ustekinumab have already been evaluated during the review of the initial application (see "Review Report for Stelara Subcutaneous Injection 45 mg Syringe" [November 10, 2010]). The data showed that the dosing regimen proposed in the current application provides an adequate safety margin based on systemic exposure. Thus, no new toxicity data have been submitted for the current application.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted evaluation data, in the form of the results from global studies (CRD3001, CRD3002, CRD3003). In these studies, concentrations of ustekinumab and anti-ustekinumab antibodies in serum were measured using an electrochemiluminescent immunoassay. The lower limit of quantification (LLOQ) for ustekinumab in serum was 16.88 ng/mL.

6.2 Clinical pharmacology

6.2.1 Foreign phase I study (CTD 5.3.1.2.1, Study ID NAP1002 [June 2014 to December 2014] [Reference data])

This study evaluated the pharmacokinetics of ustekinumab following a single intravenous dose in non-Japanese healthy adults aged between 18 and 55 years (target sample size, 140 subjects [70 per group]).

Subjects received a single 6 mg/kg intravenous ustekinumab infusion of either a 5 mg/mL or 90 mg/mL formulation.[1)]

All of 140 treated subjects (70 per group) were included in the pharmacokinetic and safety analysis sets.

The pharmacokinetic parameters of ustekinumab (all values in mean ± standard deviation [SD]):
In the 5 mg/mL formulation group, AUC_∞ was 3132.4 ± 690.2 μg·day/mL and the half-life was 24.7 ± 6.2 days.
In the 90 mg/mL formulation group, AUC_∞ was 3218.3 ± 661.1 μg·day/mL and the half-life was 25.1 ± 6.1 days.

Safety results:
The incidence of adverse events was 57.1% (40 of 70 subjects) in both formulation groups, and the incidences of adverse drug reactions were 27.1% (19 of 70 subjects) in the 5 mg/mL formulation group and 35.7% (25 of 70 subjects) in the 90 mg/mL formulation group. Adverse events reported by ≥5% of subjects in either group are shown in Table 2.

Table 2. Adverse events reported by ≥5% of subjects in either group

	5 mg/mL formulation (N = 70)	90 mg/mL formulation (N = 70)
Any adverse event	**57.1 (40)**	**57.1 (40)**
Headache	**12.9 (9)**	**12.9 (9)**
Nausea	**8.6 (6)**	**7.1 (5)**
Back pain	**7.1 (5)**	**4.3 (3)**
Vomiting	**5.7 (4)**	**2.9 (2)**
Vessel puncture site haemorrhage	**2.9 (2)**	**7.1 (5)**
Upper respiratory tract infection	**1.4 (1)**	**8.6 (6)**
Oropharyngeal pain	**1.4 (1)**	**5.7 (4)**

MedDRA ver.17.1 Incidence % (n)

Adverse drug reactions reported by ≥5% of subjects in either group were back pain (7.1% [5 of 70 subjects] in the 5 mg/mL formulation group, 2.9% [2 of 70 subjects] in the 90 mg/mL formulation group), headache (5.7% [4 of 70 subjects] in the 5 mg/mL formulation group, 8.6% [6 of 70 subjects] in the 90 mg/mL formulation group), and upper respiratory tract infection (0% [0 of 70 subjects] in the 5 mg/mL formulation group, 7.1% [5 of 70 subjects] in the 90 mg/mL formulation group).

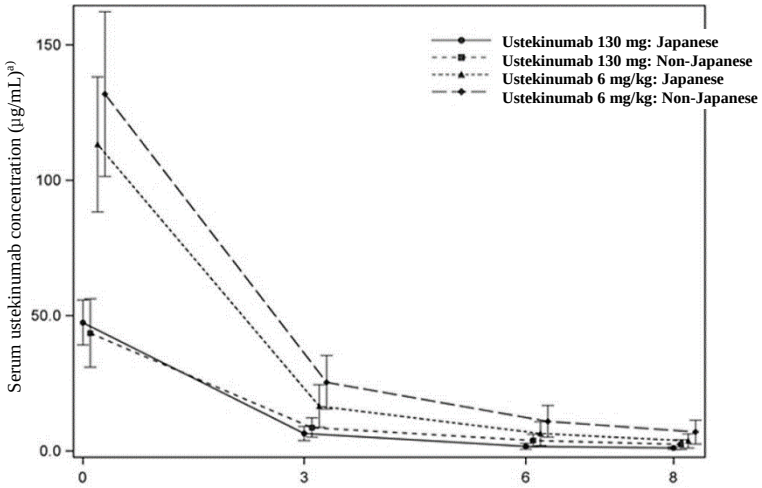
There were no deaths or discontinuations due to adverse events. As a serious adverse event, abortion occurred in 1 subject in the 90 mg/mL formulation group, and this event was classified as an adverse drug reaction.

6.2.2 Global phase III study (CTD 5.3.5.1.1, Study ID CRD3001 [June 2011 to July 2013], "Study 3001")
See Section 7.1 for a brief description of the study.

The pharmacokinetics of ustekinumab were evaluated in patients aged ≥18 years with moderately to severely active CD who had failed or were intolerant to prior anti-TNF therapy. Figure 1 shows serum ustekinumab

[1)] The 5 mg/mL intravenous formulation is proposed for marketing. A stability issue was found with an earlier 5 mg/mL intravenous formulation in global phase III studies (CRD3001, CRD3002, CRD3003), and the studies were interrupted in [redacted] 20[redacted] [see Sections 7.1 to 7.3]. It was decided to use a 90 mg/mL subcutaneous formulation for intravenous administration as an alternative to the 5 mg/mL formulation, and the studies were restarted about 1 month later.

concentrations over time in Japanese and non-Japanese subjects following a single dose of ustekinumab 130 mg or 6 mg/kg (260 mg [body weight ≤55 kg], 390 mg [body weight >55 kg and ≤85 kg], 520 mg [body weight >85 kg]), infused intravenously over a period of ≥1 hour.



Japanese: 19 subjects in the ustekinumab 130 mg group, 19 subjects in the ustekinumab 6 mg/kg group
Non-Japanese: 224 subjects in the ustekinumab 130 mg group, 226 subjects in the ustekinumab 6 mg/kg group

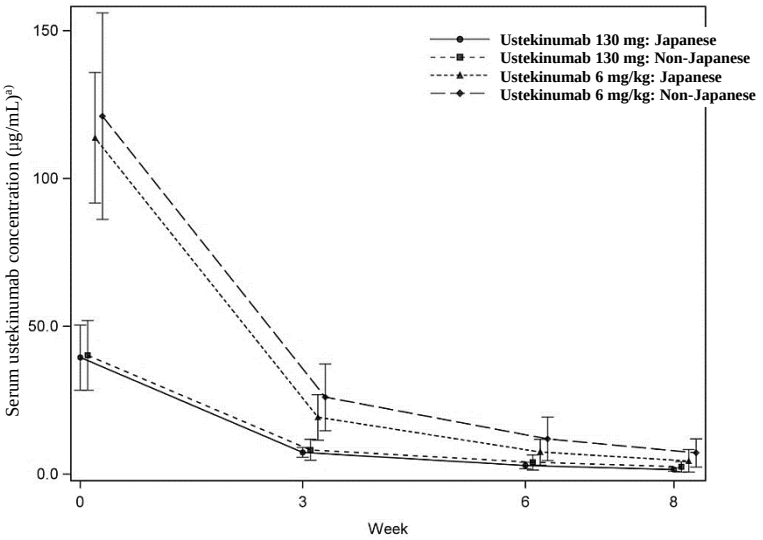
Figure 1. Serum ustekinumab concentrations over time in Japanese and non-Japanese subjects [b)]

a) Mean ± SD
b) This analysis excluded patients enrolled before study suspension [see Section 7.1] and patients with a pre-dose serum ustekinumab concentration being ≥5% of the concentration at 1 hour post-dose.

6.2.3 Global phase III study (CTD 5.3.5.1.2, Study ID CRD3002 [June 2011 to October 2014], "Study 3002")

See Section 7.2 for a brief description of the study.

The pharmacokinetics of ustekinumab were evaluated in patients aged ≥18 years who had moderately to severely active CD. Figure 2 shows serum ustekinumab concentrations over time in Japanese and non-Japanese subjects following a single dose of ustekinumab 130 mg or 6 mg/kg (260 mg [body weight ≤55 kg], 390 mg [body weight >55 kg and ≤85 kg], 520 mg [body weight >85 kg]), infused intravenously over a period of ≥1 hour.



Japanese: 8 subjects in the ustekinumab 130 mg group, 9 subjects in the ustekinumab 6 mg/kg group
Non-Japanese: 199 subjects in the ustekinumab 130 mg group, 197 subjects in the ustekinumab 6 mg/kg group

Figure 2. Serum ustekinumab concentrations over time in Japanese and non-Japanese subjects [b)]

a) Mean ± SD

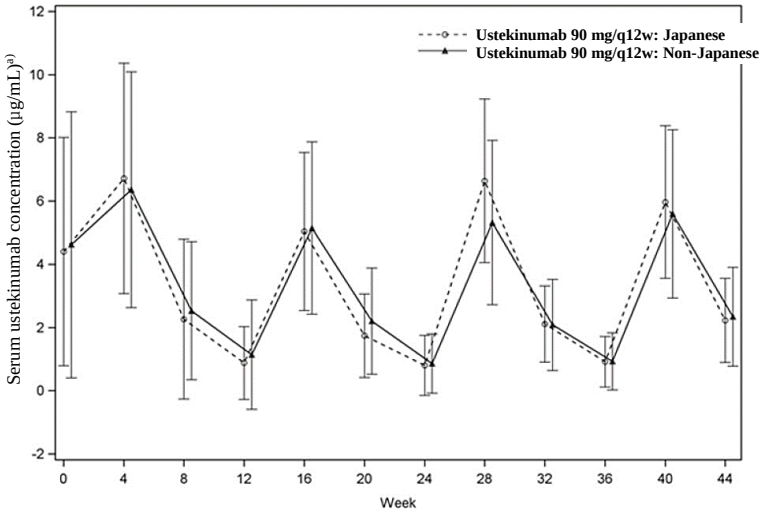
b) The analysis excluded patients enrolled before study suspension [see Section 7.1] and patients with a pre-dose serum ustekinumab concentration being ≥5% of the concentration at 1 hour post-dose.

6.2.4 Global phase III study (CTD 5.3.5.1.3-1, Study ID CRD3003 [September 2011 to June 2015], "Study 3003")

See Section 7.3 for a brief description of the study.

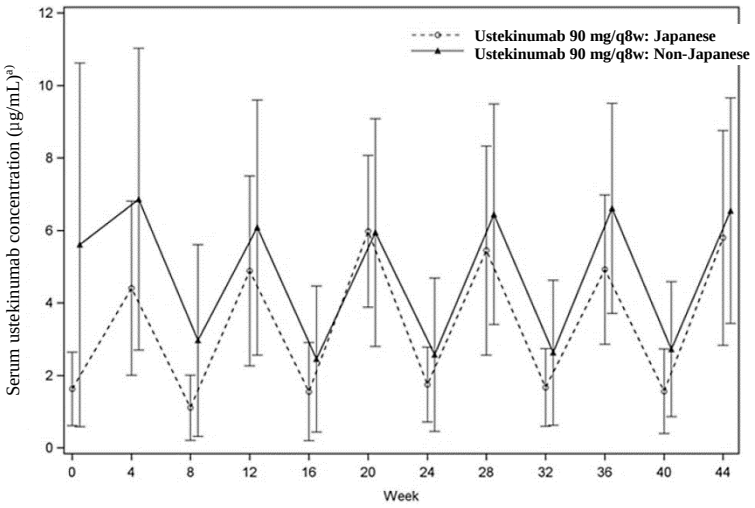
The pharmacokinetics of ustekinumab were evaluated in patients with CD who were in clinical response to intravenous ustekinumab (130 mg or 6 mg/kg) in Study 3001 or 3002.

The following figures show serum ustekinumab concentrations over time in Japanese and non-Japanese subjects following subcutaneous administration of ustekinumab 90 mg every 12 weeks (90 mg/q12w group [Figure 3]) or every 8 weeks (90 mg/q8w group [Figure 4]) through Week 44. (The final dose was administered at Week 36 in the 90 mg/q12w group and at Week 40 in the 90 mg/q8w group).



8 Japanese subjects, 124 non-Japanese subjects

Figure 3. Serum ustekinumab concentrations over time in Japanese and non-Japanese subjects in the ustekinumab 90 mg/q12w group
a) Mean ± SD



9 Japanese subjects, 122 non-Japanese subjects

Figure 4. Serum ustekinumab concentrations over time in Japanese and non-Japanese subjects in the ustekinumab 90 mg/q8w group
a) Mean ± SD

6.R Outline of the review conducted by PMDA

The applicant's explanation of differences in the pharmacokinetics of ustekinumab between Japanese and non-Japanese subjects:

A high interindividual variability was found in serum ustekinumab concentrations over time following intravenous administration of ustekinumab (Studies 3001 and 3002) and following subcutaneous administration of ustekinumab (Study 3003), but the distribution of serum ustekinumab concentration over

time in Japanese subjects is similar to that in non-Japanese subjects. Thus, there should be no clinically relevant major differences in the pharmacokinetics of ustekinumab between Japanese and non-Japanese subjects.

PMDA accepted the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from 3 global phase III studies (CRD3001, CRD3002, CRD3003).

CDAI score used for efficacy assessment and the response/remission criteria are shown in Table 3 and Table 4, respectively.

Table 3. CDAI score

CDAI (The sum of the following items, each multiplied by a factor)		Factor
Liquid stools	Total number of soft or liquid stools in the previous week	×2
Abdominal pain	Abdominal pain in the previous week (7-day total of daily abdominal pain scores) 0 = none, 1 = mild, 2 = moderate, 3 = severe	×5
General well-being	General well-being, subjectively assessed in the previous week (7-day total of daily general well-being scores) 0 = well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible	×7
Extra-intestinal manifestations	Number of the following categories currently present 1) arthritis/arthralgia, 2) iritis/uveitis, 3) erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, 4) anal fissure, fistula, or perirectal abscess, 5) other fistula, 6) fever over 37.8°C during the previous week	×20
Antidiarrheals	Antidiarrheal or opioid receptor agonist use 0 = No, 1 = Yes	×30
Abdominal mass	0 = None, 2 = Questionable, 5 = Definite	×10
Hematocrit (Ht)	Males: 47 − Ht Females: 42 − Ht	×6
Body weight	100 × (1 − body weight of patient/standard body weight)	×1

Table 4. CDAI response/remission criteria

CR (clinical response)	A ≥100-point decrease from baseline in CDAI score (Subjects with a baseline CDAI score of 220 to 248 were considered to be in clinical response if a CDAI score of <150 was attained.)
Clinical remission	CDAI score <150
Loss of response	CDAI score ≥220 and a ≥100-point increase from baseline[a)] in CDAI score

a) Week 0 of Study 3003 (Week 8 of Study 3001 or 3002)

7.1 Global phase III study (CTD 5.3.5.1.1, Study ID CRD3001 [June 2011 to July 2013], "Study 3001")

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 178 sites in 23 countries (13 sites in Japan) to evaluate the efficacy and safety of ustekinumab in patients aged ≥18 years with moderately to severely active CD who had failed or were intolerant to anti-TNF therapy (Table 5) (target sample size, 675 subjects [225 per group]).

Table 5. Key inclusion/exclusion criteria for activity of CD and previous treatment

● Patients with CD who met all of the following criteria were included:
· CDAI score of 220 to 450
· Received infliximab, adalimumab, or certolizumab pegol, and
a) did not respond initially (primary non-response),
b) responded initially but then lost response (secondary non-response), or
c) were intolerant to the medication.
· The following prior medications had been administered at a stable dose, or had been discontinued, for at least 3 weeks prior to baseline
Oral 5-ASA preparations
Oral corticosteroids (at a prednisone-equivalent dose of ≤40 mg/day or ≤9 mg/day of budesonide)
Antibiotics being used as a treatment of CD
· Patients receiving immunomodulators (AZA, 6-MP, or MTX) must have been taking them for ≥12 weeks, and on a stable dose for a least 4 weeks prior to baseline.
● Patients who had received the following agents within the specified period were excluded:
· Intravenous corticosteroids within 3 weeks before baseline
· Cyclosporine, tacrolimus, etc., within 6 weeks before baseline
· Anti-TNF agents within 8 weeks before baseline

Subjects received a single intravenous infusion of placebo or ustekinumab 130 mg or 6 mg/kg (260 mg [body weight ≤55 kg], 390 mg [body weight >55 kg and ≤85 kg], 520 mg [body weight >85 kg]) over a period of ≥1 hour.

After the initiation of the study, a stability issue was found with the intravenous formulation, and the study was interrupted in [redacted] 20[redacted], but restarted about 1 month later.[1)]

Of 769 randomized subjects, 28 were randomized prior to the study interruption (9 in the placebo group, 9 in the ustekinumab 130 mg group, 10 in the ustekinumab 6 mg/kg). The efficacy analysis set included 741 subjects (247 in the placebo group, 245 in the ustekinumab 130 mg group, 249 in the ustekinumab 6 mg/kg group), excluding the 28 subjects.[2)] The safety analysis set included 768 subjects (254 in the placebo group, 255 in the ustekinumab 130 mg group, 259 in the ustekinumab 6 mg/kg group), excluding 1 subject who received no study drug in the placebo group.[3)]

Four subjects were withdrawn from the study prior to the study interruption (2 in the placebo group [consent withdrawal for both subjects], 2 in the ustekinumab 130 mg group [consent withdrawal; and lost to follow-up, 1 subject each]). After the study restart, 33 subjects were withdrawn from the study (10 in the placebo group, 9 in the ustekinumab 130 mg group, 14 in the ustekinumab 6 mg/kg group); the reasons for withdrawals were consent withdrawal (21 subjects [6 in the placebo group, 5 in the ustekinumab 130 mg group, 10 in the ustekinumab 6 mg/kg group), lost to follow-up (5 subjects [2 in the placebo group, 1 in the ustekinumab 130 mg group, 2 in the ustekinumab 6 mg/kg group), and others (7 subjects [2 in the placebo group, 3 in the ustekinumab 130 mg group, 2 in the ustekinumab 6 mg/kg group).

[2)] The applicant considered that the knowledge of this issue might bias efficacy assessments, and decided to exclude subjects randomized prior to the study interruption (no Japanese patients were randomized prior to the study interruption) from the primary efficacy analysis set.

[3)] One subject who was randomized to the placebo group, but actually received ustekinumab 36.9 mg was analyzed as the 130 mg group, 1 subject who was randomized to the 130 mg group, but actually received 3.5 mg/kg was analyzed as the 6 mg/kg group, and 1 subject who was randomized to the 6 mg/kg group, but actually received 3.1 mg was analyzed as the 130 mg/kg group.

The primary efficacy endpoint was clinical response (CR) rate at Week 6 [Table 6]; the results showed the superiority of both 130 mg and 6 mg/kg of ustekinumab over placebo (two-sided significance level of 5%, Cochran-Mantel Haenszel test, a closed testing procedure for multiplicity adjustment).

Table 6. CR rate at Week 6 (Efficacy analysis set [Entire study population])

	Induction phase (Single intravenous infusion)		
	Placebo	Ustekinumab	
		130 mg	6 mg/kg
No. of subjects analyzed	247	245	249
CR rate[a] % (n)	21.5 (53)	34.3 (84)	33.7 (84)
Difference from placebo [95% CI]	–	12.8 [5.0, 20.7]	12.3 [4.5, 20.1]
P-value[b), c)]	–	0.002	0.003

a) Subjects with a missing CDAI score at Week 6 were considered to have failed to achieve CR.
b) Cochran-Mantel Haenszel test (stratified by study region [Asia, Eastern Europe, or rest of world], CDAI score [≤300 or >300] and initial response to TNF antagonist therapy [yes or no])
c) Two-sided significance level of 5%. A closed testing procedure (if the ustekinumab 6 mg/kg group was statistically significantly different from the placebo group, then the ustekinumab 130 mg group was compared with the placebo group) was used for multiplicity adjustment.

Safety results:

In 768 subjects who received study drug, the incidences of adverse events through Week 8 were 65.4% (166 of 254 subjects) in the placebo group, 65.9% (168 of 255 subjects) in the ustekinumab 130 mg group, and 64.9% (168 of 259 subjects) in the ustekinumab 6 mg/kg group, and the incidences of adverse drug reactions were 26.4% (67 of 254 subjects) in the placebo group, 25.5% (65 of 255 subjects) in the ustekinumab 130 mg group, and 28.6% (74 of 259 subjects) in the ustekinumab 6 mg/kg group. In the Japanese population (56 subjects), the incidences of adverse events were 61.1% (11 of 18 subjects) in the placebo group, 52.6% (10 of 19 subjects) in the ustekinumab 130 mg group, and 47.4% (9 of 19 subjects) in the ustekinumab 6 mg/kg group, and the incidences of adverse drug reactions were 16.7% (3 of 18 subjects) in the placebo group, 10.5% (2 of 19 subjects) in the ustekinumab 130 mg group, and 10.5% (2 of 19 subjects) in the ustekinumab 6 mg/kg group.

In the entire study population, adverse events reported by ≥2% of subjects in any group through Week 8 are shown in Table 7, and adverse drug reactions reported by ≥2% of subjects in any group are shown in Table 8.

Table 7. Adverse events reported by ≥2% of subjects in any group (all subjects who received study drug)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 254)	Ustekinumab	
		130 mg (N = 255)	6 mg/kg (N = 259)
Any adverse event	65.4 (166)	65.9 (168)	64.9 (168)
Headache	8.7 (22)	7.8 (20)	7.7 (20)
Arthralgia	7.5 (19)	11.0 (28)	5.8 (15)
Nausea	7.1 (18)	7.8 (20)	5.8 (15)
Pyrexia	5.9 (15)	5.9 (15)	5.8 (15)
Abdominal pain	5.5 (14)	3.9 (10)	5.4 (14)
Nasopharyngitis	5.5 (14)	4.7 (12)	4.6 (12)
Upper respiratory tract infection	3.5 (9)	4.7 (12)	3.9 (10)
Crohn's disease	11.4 (29)	5.9 (15)	2.3 (6)
Vomiting	3.5 (9)	3.5 (9)	4.2 (11)
Fatigue	5.1 (13)	2.4 (6)	3.9 (10)
Oropharyngeal pain	2.8 (7)	1.2 (3)	3.1 (8)
Rash	2.8 (7)	2.0 (5)	2.7 (7)
Back pain	2.4 (6)	1.2 (3)	2.7 (7)
Diarrhoea	3.5 (9)	0.8 (2)	1.2 (3)
Constipation	0.8 (2)	2.7 (7)	0.8 (2)
Cough	2.8 (7)	3.1 (8)	0.4 (1)

Sinusitis	**2.4 (6)**	**1.2 (3)**	**0.4 (1)**

MedDRA ver.17.1 Incidence % (n)

Table 8. Adverse drug reactions reported by ≥2% of subjects in any group (All subjects who received study drug)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 254)	Ustekinumab	
		130 mg (N = 255)	6 mg/kg (N = 259)
Any adverse drug reaction	26.4 (67)	25.5 (65)	28.6 (74)
Headache	2.4 (6)	2.7 (7)	3.5 (9)
Fatigue	2.8 (7)	0 (0)	2.3 (6)
Nausea	3.5 (9)	0.8 (2)	2.3 (6)
Vomiting	0.8 (2)	0.8 (2)	2.3 (6)
Abdominal pain	2.4 (6)	0 (0)	1.2 (3)

MedDRA ver.17.1 Incidence % (n)

In the Japanese population, adverse events reported by ≥2 subjects in any group through Week 8 are shown in Table 9. No adverse drug reactions were reported by ≥2 subjects in any group.

Table 9. Adverse events reported by ≥2 subjects in any group (Japanese population)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 18)	Ustekinumab	
		130 mg (N = 19)	6 mg/kg (N = 19)
Any adverse event	61.1 (11)	52.6 (10)	47.4 (9)
Pyrexia	5.6 (1)	0 (0)	10.5 (2)
Nasopharyngitis	0 (0)	15.8 (3)	5.3 (1)
Nausea	5.6 (1)	10.5 (2)	0 (0)
Abdominal pain upper	0 (0)	10.5 (2)	0 (0)
Crohn's disease	11.1 (2)	0 (0)	0 (0)

MedDRA ver.17.1 Incidence % (n)

No deaths were reported. The incidences of serious adverse events were 7.1% (18 of 254 subjects) in the placebo group, 5.5% (14 of 255 subjects) in the ustekinumab 130 mg group, and 6.9% (18 of 259 subjects) in the ustekinumab 6 mg/kg group (Table 10-1), and the incidences of serious adverse drug reactions were 0.8% (2 of 254 subjects) in the placebo group, 0.4% (1 of 255 subjects) in the ustekinumab 130 mg group, and 1.9% (5 of 259 subjects) in the ustekinumab 6 mg/kg group (Table 10-2). The outcomes of the serious adverse drug reactions were all reported as "resolved."

Table 10-1. Serious adverse events (Entire study population)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 254)	Ustekinumab	
		130 mg (N = 255)	6 mg/kg (N = 259)
Serious adverse events	7.1% (n = 18)	5.5% (n = 14)	6.9% (n = 18)
Event term (No. of subjects with event)	Crohn's disease (8) Crohn's disease* (2) Pneumonia viral (1) Malnutrition (1) Diarrhoea (1) Large intestine perforation (1) Hypokalaemia (1) Anal abscess (1) Diarrhoea and pyrexia (1) Infected fistula, postoperative abscess,* intracardiac thrombus,* and dental caries* (1)	Crohn's disease (5) Gastroenteritis viral (1) Vulval abscess (1) Pelvic abscess (1) Nephrolithiasis (1) Pyelonephritis (1) Abscess intestinal (1) Phlebitis superficial (1) Crohn's disease, dehydration, asthma,* and pulmonary embolism* (1) Crohn's disease, hypocalcaemia, hypokalaemia, hypomagnesaemia, and blood electrolytes abnormal* (1)	Crohn's disease (3) Clostridial infection (1) Meningitis listeria (1) Lymphocele (1) Hypersensitivity (1) Colonic fistula (1) Road traffic accident (1) Gastric ulcer haemorrhage (1) Small intestinal obstruction (1) Cholangitis (1) Abscess intestinal (1) Crohn's disease and abdominal pain (1) Crohn's disease and peritonitis (1) Perineal abscess and female genital tract fistula (1) Atrial fibrillation and cardiac failure (1) Escherichia sepsis, intervertebral discitis, and multiple myeloma* (1)

MedDRA ver.17.1
*: Events occurring after Week 8 in subjects who did not enter Study 3003.

Table 10-2. Serious adverse drug reactions (Entire study population)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 254)	Ustekinumab	
		130 mg (N = 255)	6 mg/kg (N = 259)
Serious adverse drug reactions	0.8% (n = 2)	0.4% (n = 1)	1.9% (n = 5)
Event term (No. of subjects with event)	Pneumonia viral (1) Infected fistula and postoperative abscess* (1)	Abscess intestinal (1)	Meningitis listeria (1) Colonic fistula (1) Multiple myeloma* (1) Cholangitis (1) Abscess intestinal (1)

MedDRA ver.17.1
*: Events occurring after Week 8 in subjects who did not enter Study 3003.

The incidences of adverse events leading to discontinuation were 6.3% (16 of 254 subjects) in the placebo group, 1.6% (4 of 255 subjects) in the ustekinumab 130 mg group, and 2.7% (7 of 259 subjects) in the ustekinumab 6 mg/kg group (Table 11-1). The incidences of adverse drug reactions leading to discontinuation were 1.6% (4 of 254 subjects) in the placebo group, 0.4% (1 of 255 subjects) in the ustekinumab 130 mg group, and 1.2% (3 of 259 subjects) in the ustekinumab 6 mg/kg group (Table 11-2), and the outcomes of those events were reported as "resolved" except for 1 case of leukocytoclastic vasculitis (unresolved).

Table 11-1. Adverse events leading to discontinuation (Entire study population)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 254)	Ustekinumab	
		130 mg (N = 255)	6 mg/kg (N = 259)
Adverse events	6.3% (n = 16)	1.6% (n = 4)	2.7% (n = 7)
Event term (No. of subjects with event)	Crohn's disease (12) Crohn's disease* (1) Infected fistula (1) Diabetic foot (1) Pregnancy (1)	Crohn's disease (2) Abscess intestinal (1) Pyrexia (1)	Crohn's disease (1) Meningitis listeria (1) Perineal abscess (1) Colonic fistula (1) Blood immunoglobulin E increased (1) Leukocytoclastic vasculitis (1) Inguinal hernia (1)

MedDRA ver.17.1

*: Events occurring after Week 8 in subjects who did not enter Study 3003.

Table 11-2. Adverse drug reactions leading to discontinuation (Entire study population)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 254)	Ustekinumab	
		130 mg (N = 255)	6 mg/kg (N = 259)
Adverse drug reactions	1.6% (n = 4)	0.4% (n = 1)	1.2% (n = 3)
Event term (No. of subjects with event)	Crohn's disease (2) Infected fistula (1) Diabetic foot (1)	Abscess intestinal (1)	Meningitis listeria (1) Colonic fistula (1) Leukocytoclastic vasculitis (1)

MedDRA ver.17.1

*: Events occurring after Week 8 in subjects who did not enter Study 3003.

In the Japanese population, serious adverse events occurred in 2 subjects in the placebo group (Crohn's disease), but a causal relationship to study drug was ruled out for both cases. In the Japanese population, an adverse event leading to discontinuation occurred in 1 subject in the placebo group (Crohn's disease), but its causal relationship to study drug was ruled out.

7.2 Global phase III study (CTD 5.3.5.1.2, Study ID CRD3002 [June 2011 to October 2014], "Study 3002")

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 175 sites in 23 countries (16 sites in Japan), to evaluate the efficacy and safety of ustekinumab in patients aged ≥18 years who had moderately to severely active CD (Table 12) (target sample size, 600 subjects [200 per group]).

Table 12. Key inclusion/exclusion criteria for activity of CD and previous treatment

● Patients with CD who met all of the following criteria were included:
· CDAI score of 220 to 450
· At least one of the following:
CRP >0.3 mg/dL or fecal calprotectin >250 mg/kg or endoscopy with evidence of active Crohn's disease within 3 months prior to baseline
·Patients had failed to respond to or tolerate corticosteroids or immunomodulators (AZA, 6-MP, MTX), or were corticosteroid-dependent.
·Patients had not previously demonstrated inadequate response or intolerance to anti-TNF therapy.
· The following prior medications had been administered at a stable, or had been discontinued, for at least 3 weeks prior to baseline
Oral 5-ASA preparations
Oral corticosteroids (at a prednisone-equivalent dose of ≤40 mg/day or ≤9 mg/day of budesonide)
Antibiotics being used as a treatment of CD
· Patients receiving immunomodulators (AZA, 6-MP, MTX) must have been taking them for ≥12 weeks, and on a stable dose for a least 4 weeks prior to baseline.
● Patients who had received the following agents within the specified period were excluded.
· Intravenous corticosteroids within 3 weeks before baseline
· Cyclosporine, tacrolimus, etc., within 6 weeks before baseline
· Anti-TNF agents within 8 weeks before baseline

Subjects received a single intravenous infusion of placebo or ustekinumab 130 mg or 6 mg/kg (260 mg [body weight ≤55 kg], 390 mg [body weight >55 kg and ≤85 kg], 520 mg [body weight >85 kg]) over a period of ≥1 hour.

After the initiation of the study, a stability issue was found with the intravenous formulation, and the study was interrupted in [redacted] 20[redacted], but restarted about 1 month later.[1)]

Of 640 randomized subjects, 12 subjects were randomized prior to the study interruption (4 in the placebo group, 4 in the ustekinumab 130 mg group, 4 in the ustekinumab 6 mg/kg group). Exclusion of these 12 subjects resulted in 628 subjects. In addition, 1 subject in the placebo group was excluded because data accuracy could not be assured. As a result, 627 subjects (209 in the placebo group, 209 in the ustekinumab 130 mg group, 209 in the ustekinumab 6 mg/kg group) were included in the efficacy analysis set. The safety analysis set consisted of 639 subjects who received study drug (212 in the placebo group, 216 in the ustekinumab 130 mg group, 211 in the ustekinumab 6 mg/kg group).[4)]

Two subjects were withdrawn from the study prior to the study interruption (1 in the placebo group [lost to follow-up], 1 in the ustekinumab 6 mg/kg group [consent withdrawal]) and 23 subjects were withdrawn from the study after the study restart (12 in the placebo group, 9 in the ustekinumab 130 mg group, 2 in the ustekinumab 6 mg/kg group). The reasons for withdrawals after the study restart were consent withdrawal (15 subjects [7 in the placebo group, 7 in the ustekinumab 130 mg group, 1 in the ustekinumab 6 mg/kg group]), lost to follow-up (7 subjects [4 in the placebo group, 2 in the ustekinumab 130 mg group, 1 in the ustekinumab 6 mg/kg group]), and others (1 in the placebo group).

The primary efficacy endpoint was CR rate at Week 6 [Table 13]; the results showed the superiority of both 130 mg and 6 mg/kg of ustekinumab over placebo (two-sided significance level of 5%, Cochran-Mantel Haenszel test, a closed testing procedure for multiplicity adjustment).

Table 13. CR rate at Week 6 (Efficacy analysis set [Entire study population])

	Induction phase (Single intravenous infusion)		
	Placebo	Ustekinumab	
		130 mg	6 mg/kg
N	209	209	209
CR rate[a)] % (n)	28.7 (60)	51.7 (108)	55.5 (116)
Difference from placebo [95% CI]	—	23.0 [13.8, 32.1]	26.8 [17.7, 35.9]
P-value[b), c)]	—	< 0.001	< 0.001

a) Subjects with a missing CDAI score at Week 6 were considered to have failed to achieve CR.
b) Cochran-Mantel Haenszel test (stratified by study region [Asia, Eastern Europe, or rest of world] and CDAI score [≤300 or >300])
c) Two-sided significance level of 5%. A closed testing procedure (if the ustekinumab 6 mg/kg group was statistically significantly different from the placebo group, then the ustekinumab 130 mg group was compared with the placebo group) was used for multiplicity adjustment.

Safety results:

[4)] One subject who was randomized to the placebo group, but actually received ustekinumab 130 mg was analyzed as the 130 mg group, and 2 subjects who were randomized to the 6 mg/kg group, but actually received ustekinumab 130 mg were analyzed as the 130 mg group.

In 639 subjects who received study drug, the incidences of adverse events through Week 8 were 55.2% (117 of 212 subjects) in the placebo group, 49.1% (106 of 216 subjects) in the ustekinumab 130 mg group, and 55.9% (118 of 211 subjects) in the ustekinumab 6 mg/kg group, and the incidences of adverse drug reactions were 17.5% (37 of 212 subjects) in the placebo group, 13.0% (28 of 216 subjects) in the ustekinumab 130 mg group, and 12.3% (26 of 211 subjects) in the ustekinumab 6 mg/kg group. In the Japanese population (26 subjects), the incidences of adverse events were 44.4% (4 of 9 subjects) in the placebo group, 37.5% (3 of 8 subjects) in the ustekinumab 130 mg group, and 55.6% (5 of 9 subjects) in the ustekinumab 6 mg/kg group, and the incidences of adverse drug reactions were 22.2% (2 of 9 subjects) in the placebo group, 12.5% (1 of 8 subjects) in the ustekinumab 130 mg group, and 0% (0 of 9 subjects) in the ustekinumab 6 mg/kg group.

In the entire study population, adverse events reported by ≥2% of subjects in any group are shown in Table 14. Adverse drug reactions reported by ≥2% of subjects in any group were headache (2.8% [6 of 212 subjects] in the placebo group, 3.2% [7 of 216 subjects] in the ustekinumab 130 mg group, 2.8% [6 of 211 subjects] in the ustekinumab 6 mg/kg group).

Table 14. Adverse events reported by ≥2% of subjects in any group (All subjects who received study drug)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 212)	Ustekinumab	
		130 mg (N = 216)	6 mg/kg (N = 211)
Any adverse event	55.2 (117)	49.1 (106)	55.9 (118)
Nasopharyngitis	4.7 (10)	4.6 (10)	6.6 (14)
Nausea	2.4 (5)	3.2 (7)	5.2 (11)
Pyrexia	4.7 (10)	2.8 (6)	5.2 (11)
Headache	6.6 (14)	9.3 (20)	4.7 (10)
Arthralgia	1.9 (4)	3.7 (8)	4.7 (10)
Abdominal pain	3.3 (7)	2.3 (5)	4.7 (10)
Vomiting	1.4 (3)	2.3 (5)	4.3 (9)
Crohn's disease	4.7 (10)	3.7 (8)	3.8 (8)
Upper respiratory tract infection	5.2 (11)	1.9 (4)	3.3 (7)
Cough	1.9 (4)	0.9 (2)	3.3 (7)
Bronchitis	2.8 (6)	1.4 (3)	1.9 (4)
Back pain	1.4 (3)	2.8 (6)	1.4 (3)
Dyspepsia	2.4 (5)	1.4 (3)	0.9 (2)
Myalgia	1.9 (4)	2.3 (5)	0.5 (1)

MedDRA ver.17.1 Incidence % (n)

In the Japanese population, adverse events reported by ≥2 subjects in any group are shown in Table 15. Adverse drug reactions reported by ≥2 subjects in any group were pyrexia (2 subjects in the placebo group).

Table 15. Adverse events reported by ≥2 subjects in any group (Japanese population)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 9)	Ustekinumab	
		130 mg (N = 8)	6 mg/kg (N = 9)
Any adverse event	44.4 (4)	37.5 (3)	55.6 (5)
Nasopharyngitis	22.2 (2)	12.5 (1)	11.1 (1)
Pyrexia	22.2 (2)	12.5 (1)	0 (0)

MedDRA ver.17.1 Incidence % (n)

No deaths were reported. The incidences of serious adverse events were 7.1% (15 of 212 subjects) in the placebo group, 4.6% (10 of 216 subjects) in the ustekinumab 130 mg group, and 4.3% (9 of 211 subjects) in the ustekinumab 6 mg/kg group (Table 16-1). Serious adverse drug reactions occurred in 0.5% (1 of 212) of

subjects in the placebo group and 0.9% (2 of 216) of subjects in the ustekinumab 130 mg group (Table 16-2). The outcomes of the serious adverse drug reactions were all reported as "resolved."

Table 16-1. Serious adverse events (Entire study population)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 212)	Ustekinumab	
		130 mg (N = 216)	6 mg/kg (N = 211)
Serious adverse events	7.1% (n = 15)	4.6% (n = 10)	4.3% (n = 9)
Event term (No. of subjects with event)	Crohn's disease (3) Anal abscess* (2) Anal abscess (1) Dysmenorrhoea (1) Bile duct stone (1) Intestinal obstruction (1) Headache* (1) Pancytopenia (1) Anaemia (1) Crohn's disease and genital herpes* (1) Small intestinal obstruction and small intestinal perforation (1) Crohn's disease, atrial fibrillation, and pneumonia (1)	Crohn's disease (3) Anal abscess (2) Pneumothorax spontaneous (1) Non-cardiac chest pain (1) Crohn's disease and localised intraabdominal fluid collection* (1) Incisional hernia and impaired healing (1) Crohn's disease, diarrhoea, small intestinal obstruction, and anaemia (1)	Crohn's disease (2) Small intestinal obstruction (2) Gastroenteritis (1) Chest pain* (1) Pneumothorax spontaneous (1) Colitis (1) Pulmonary granuloma* (1)

MedDRA ver.17.1
*: Events occurring after Week 8 in subjects who did not enter Study 3003.

Table 16-2. Serious adverse drug reactions (Entire study population)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 212)	Ustekinumab	
		130 mg (N = 216)	6 mg/kg (N = 211)
Serious adverse drug reactions	0.5% (n = 1)	0.9% (n = 2)	0% (n = 0)
Event term (No. of subjects with event)	Pancytopenia (1)	Diarrhoea (1) Anal abscess (1)	None

MedDRA ver.17.1
*: Events occurring after Week 8 in subjects who did not enter Study 3003.

The incidences of adverse events leading to discontinuation were 2.4% (5 of 212 subjects) in the placebo group (Crohn's disease [2 subjects]; hepatitis C; small intestinal obstruction; and anal abscess, 1 subject each), 1.9% (4 of 216 subjects) in the ustekinumab 130 mg group (Crohn's disease [2 subjects]; chest discomfort; and anal abscess, 1 subject each), and 0.5% (1 of 211 subjects) in the ustekinumab 6 mg/kg group (rash). Adverse drug reactions leading to discontinuation occurred in 0.5% (1 of 216) of subjects in the ustekinumab 130 mg group (chest discomfort) and 0.5% (1 of 211) of subjects in the ustekinumab 6 mg/kg group (rash). The event of chest discomfort resolved and the event of rash did not resolve.

In the Japanese population, serious adverse events occurred in 2 subjects in the ustekinumab 6 mg/kg group (small intestinal obstruction; and Crohn's disease [both events resolved]), but their causal relationship to study drug was ruled out. In the Japanese population, no adverse events leading to discontinuation occurred.

7.3 Global phase III study (CTD 5.3.5.1.3-1, Study ID CRD3003 [September 2011 to June 2015], "Study 3003")

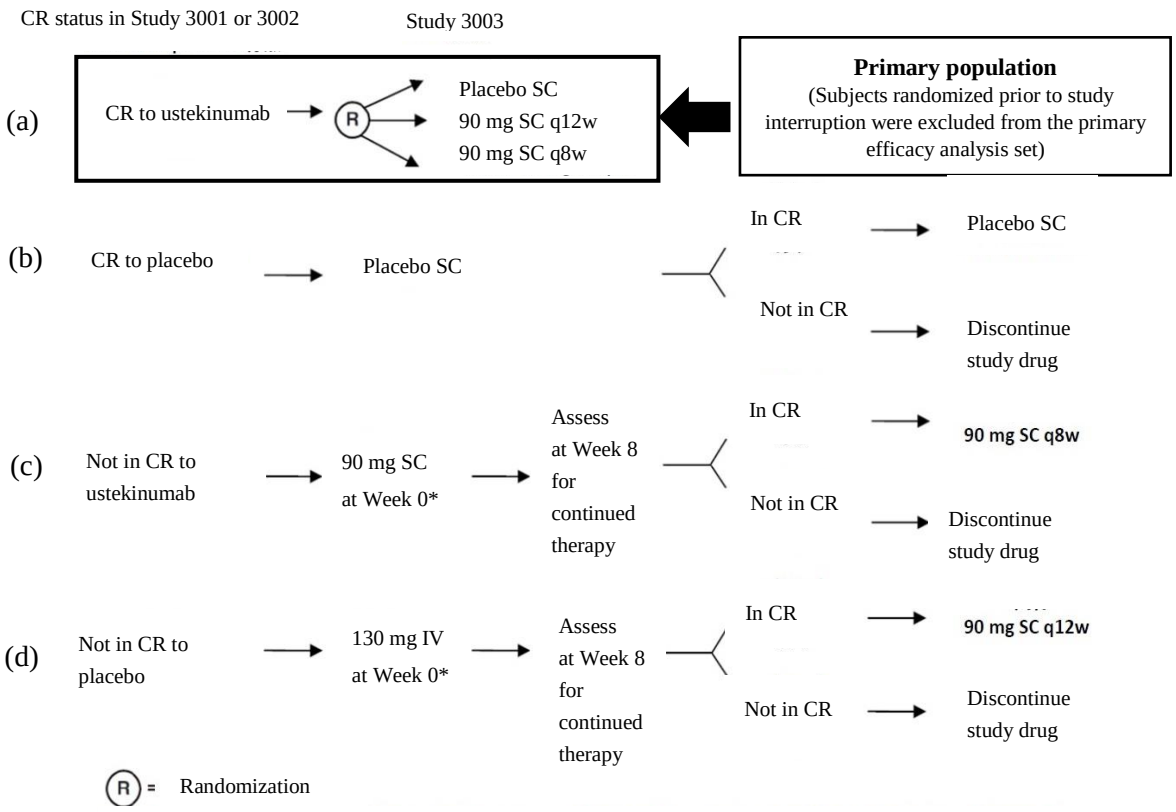
A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 260 sites in 27 countries (20 sites in Japan) to evaluate the efficacy and safety of ustekinumab maintenance therapy in patients with CD who completed Study 3001 or 3002 (Table 17) (target sample size, 1275 subjects).

Table 17. Key inclusion/exclusion criteria

● Patients with CD who met the following criteria:
・Had received study drug at Week 0 in Study 3001 or 3002 and completed Week 8 evaluation.
● Patients who met any of the following criteria since Week 0 of Study 3001 or 3002 were excluded.
・Initiation/increased dose of corticosteroids, AZA, 6-MP, or MTX
・Initiation of immunosuppressive agents such as cyclosporine and tacrolimus
・Initiation of biologic agents such as anti-TNF agents

Dosing regimen is summarized in Figure 5, and patients were assigned to treatment according to the treatment group and CR status in Study 3001 or 3002. Patients in CR to intravenous ustekinumab (130 mg or 6 mg/kg) in Study 3001 or 3002 were randomized to receive subcutaneous injections of placebo, 90 mg of ustekinumab every 12 weeks (90 mg/q12w group), or 90 mg of ustekinumab every 8 weeks (90 mg/q8w group) and followed up through Week 44 (the final dose was administered at Week 36 in the ustekinumab 90 mg/q12w group, and at Week 40 in the ustekinumab 90 mg/q8w group) [(a) in Figure 5]. These randomized subjects [(a) in Figure 5] constituted the primary population for efficacy and safety evaluation.

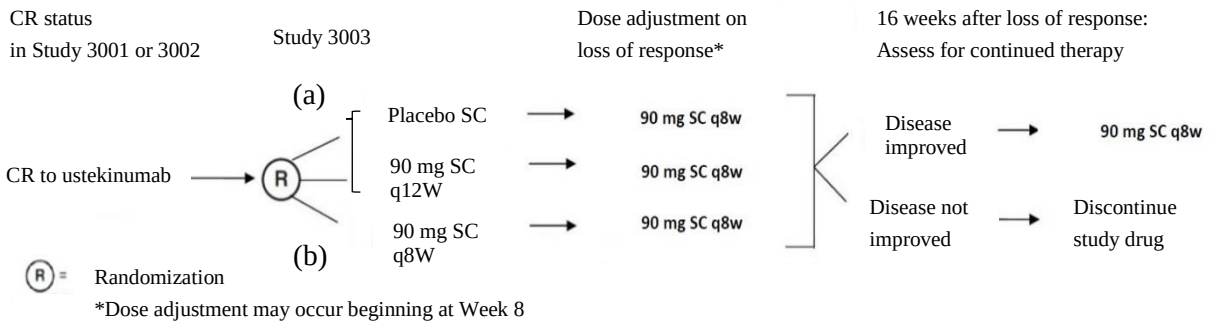
Patients in CR to placebo in Study 3001 or 3002 continued to receive subcutaneous placebo [(b) in Figure 5]. Patients not in CR to ustekinumab (130 mg or 6 mg/kg) in Study 3001 or 3002 received ustekinumab 90 mg subcutaneously at Week 0. If these patients had achieved CR at Week 8, they were to continue to receive ustekinumab 90 mg SC q8w through Week 40. If, by Week 8, these patients had not achieved CR, they were to be discontinued from further study drug administration [(c) in Figure 5]. Patients not in CR to placebo in Study 3001 or 3002 received ustekinumab 130 mg intravenously at Week 0. If these patients had achieved CR at Week 8, they were to receive ustekinumab 90 mg SC q12w. If, by Week 8, these patients had not achieved CR, they were to be discontinued from further study drug administration [(d) in Figure 5].



*To maintain the blind, both IV and SC administrations were given to all subjects not in CR to induction therapy.

Figure 5. Treatment groups and dosing regimen

Furthermore, patients in CR to intravenous ustekinumab in Study 300 or 3002 [(a) in Figure 5] were eligible for dose adjustment if they met the loss of response criteria (CDAI score ≥220 and a ≥100-point increase from baseline[Week 0 of Study 3003] in CDAI score; Table 4) at a scheduled visit between Week 8 and Week 32. Dose adjustment on loss of response is summarized in Figure 6. Patients in the placebo or 90 mg/q12w group who lost response changed treatment to ustekinumab 90 mg SC q8w [(a) in Figure 6]. Patients randomized to the 90 mg/q8w group who lost response continued to receive ustekinumab 90 mg SC q8w [(b) in Figure 6]. In all cases, patients were assessed by the investigator 16 weeks after the visit where the loss of response criteria were met, and those who had not shown improvement in their Crohn's disease activity were to be discontinued from study drug administration.



*Dose adjustment may occur beginning at Week 8

Figure 6. Dose adjustment

A subsequent study extension continued up to Week 272, but there was to be no dose adjustment in the study extension.[5)]

Study 3003 enrolled 1281 subjects who completed Study 3001 or 3002. After the initiation of the study, a stability issue was found with the intravenous formulation, and the study was interrupted in [redacted] 20[redacted], but restarted about 1 month later.

The primary efficacy analysis set consisted of 388 subjects (131 in the placebo group, 129 in the ustekinumab 90 mg/q12w group, 128 in the ustekinumab 90 mg/q8w group), after excluding 9 subjects who were enrolled prior to the study interruption from 397 subjects who were in CR to intravenous ustekinumab in Study 3001 or 3002 and were randomized in this study.[2)] The primary safety analysis set consisted of 396 subjects (133 in the placebo group, 132 in the ustekinumab 90 mg/q12w group, 131 in the ustekinumab 90 mg/q8w group), after excluding 1 subject in the ustekinumab 90 mg/q8w group who did not receive study drug from the 397 randomized subjects.

Among the randomized subjects, 2 subjects were withdrawn from the study prior to the study interruption (1 in the placebo group [consent withdrawal], 1 in the ustekinumab 90 mg/q8w group [lack of efficacy]) and 88 subjects were withdrawn from the study after the study restart (30 in the placebo group, 29 in the ustekinumab 90 mg/q12w group, 29 in the ustekinumab 90 mg/q8w group). The reasons for withdrawals after the study restart were lack of efficacy (44 subjects [15 in the placebo group, 14 in the ustekinumab 90 mg/q12w group, 15 in the ustekinumab 90 mg/q8w group]), adverse events (27 subjects [9 in the placebo group, 12 in the ustekinumab 90 mg/q12w group, 6 in the ustekinumab 90 mg/q8w group]), consent withdrawal (15 subjects [6 in the placebo group, 2 in the ustekinumab 90 mg/q12w group, 7 in the ustekinumab 90 mg/q8w group]), lost to follow-up (2 subjects [1 in the placebo group, 1 in the ustekinumab 90 mg/q8w group]), and protocol deviations (2 subjects [1 in the ustekinumab 90 mg/q12w group, 1 in the ustekinumab 90 mg/q8w group]) (some of these subjects had more than one reason). Non-randomized subjects (884 subjects; (b) (c) (d) in Figure 5) were also included in some safety analyses.[6)]

The primary efficacy endpoint was clinical remission rate at Week 44 [Table 18]; the results showed the superiority of ustekinumab 90 mg/q12w and 90 mg/q8w over placebo (two-sided significance level of 5%, Cochran-Mantel Haenszel test, a closed testing procedure for multiplicity adjustment).

[5)] Subjects were to continue to receive the same treatment regimen that they were receiving at the end of the main study (through Week 44) (either placebo or 90 mg SC ustekinumab q8W or q12W), and there was to be no dose adjustment. The study blind was maintained in the study extension until the last subject in the main study completed the Week 44 evaluations and the Week 44 analyses had been completed. After the study was unblinded, patients receiving placebo were terminated from study participation.

[6)] Of 884 non-randomized subjects, 17 subjects were enrolled prior to the study interruption. Among the non-randomized subjects, 455 subjects were withdrawn from the study, and the reasons for withdrawals were lack of efficacy (358), adverse events (46), consent withdrawal (36), lost to follow-up (13), and protocol deviations (2).

Table 18. Clinical remission rate at Week 44 (Primary efficacy analysis set)

	Maintenance phase (Subcutaneous injections)		
	Placebo	Ustekinumab	
		90 mg/q12w	90 mg/q8w
N	131	129	128
Clinical remission rate[a] % (n)	35.9 (47)	48.8 (63)	53.1 (68)
Difference from placebo [95% CI]	—	13.0 [1.1, 24.9]	17.2 [5.3, 29.2]
P-value[b), c)]	—	0.040	0.005

a) Subjects with a missing CDAI score at Week 44 or a loss of response were considered not in clinical remission.

b) Cochran-Mantel Haenszel test (stratified by clinical remission status at Week 0 of Study 3003, ustekinumab induction dose in Study 3001 or 3002, and the induction study before enrollment in Study 3003 [Study 3001, Study 3002])

c) Two-sided significance level of 5%. A closed testing procedure (if the ustekinumab 90 mg/q8w group was statistically significantly different from the placebo group, then the ustekinumab 90 mg/q12w group was compared with the placebo group) was used for multiplicity adjustment.

Safety results:

In all randomized subjects who received study drug (the primary safety analysis set), the incidences of adverse events through Week 44 or up to the time of dose adjustment were 83.5% (111 of 133 subjects) in the placebo group, 80.3% (106 of 132 subjects) in the ustekinumab 90 mg/q12w group, and 81.7% (107 of 131 subjects) in the ustekinumab 90 mg/q8w group, and the incidences of adverse drug reactions were 31.6% (42 of 133 subjects) in the placebo group, 25.8% (34 of 132 subjects) in the ustekinumab 90 mg/q12w group, and 29.8% (39 of 131 subjects) in the ustekinumab 90 mg/q8w group.

In all randomized subjects who received study drug, adverse events or adverse drug reactions reported by ≥5% of subjects in any group through Week 44 or up to the time of dose adjustment are shown in Table 19 and Table 20, respectively.

Table 19. Adverse events reported by ≥5% of subjects in any group (All randomized subjects who received study drug) [through Week 44 or up to time of dose adjustment]

	Maintenance phase (Subcutaneous injections)		
	Placebo (N = 133)	Ustekinumab	
		90 mg/q12w (N = 132)	90 mg/q8w (N = 131)
Any adverse event	83.5 (111)	80.3 (106)	81.7 (107)
Arthralgia	14.3 (19)	16.7 (22)	13.7 (18)
Crohn's disease	14.3 (19)	12.1 (16)	12.2 (16)
Headache	11.3 (15)	11.4 (15)	12.2 (16)
Nasopharyngitis	7.5 (10)	12.9 (17)	10.7 (14)
Upper respiratory tract infection	15.8 (21)	6.8 (9)	9.9 (13)
Abdominal pain	12.0 (16)	9.8 (13)	8.4 (11)
Pyrexia	7.5 (10)	8.3 (11)	6.1 (8)
Rash	3.8 (5)	3.0 (4)	5.3 (7)
Cough	2.3 (3)	3.0 (4)	5.3 (7)
Injection site erythema	0 (0)	0.8 (1)	5.3 (7)
Fatigue	4.5 (6)	6.1 (8)	4.6 (6)
Diarrhoea	5.3 (7)	8.3 (11)	3.8 (5)
Influenza	3.8 (5)	6.1 (8)	3.8 (5)
Nausea	6.8 (9)	7.6 (10)	3.1 (4)
Urinary tract infection	2.3 (3)	6.1 (8)	3.1 (4)
Vomiting	6.8 (8)	3.8 (5)	3.1 (4)

MedDRA ver.17.1 Incidence % (n)

Table 20. Adverse drug reactions reported by ≥5% of subjects in any group (All randomized subjects who received study drug) [through Week 44 or up to time of dose adjustment]

	Maintenance phase (Subcutaneous injections)		
	Placebo (N = 133)	Ustekinumab	
		90 mg/q12w (N = 132)	90 mg/q8w (N = 131)
Any adverse drug reaction	31.6 (42)	25.8 (34)	29.8 (39)
Injection site erythema	0 (0)	0.8 (1)	5.3 (7)
Upper respiratory tract infection	6.8 (9)	1.5 (2)	4.6 (6)
Arthralgia	5.3 (7)	0.8 (1)	0.8 (1)

MedDRA ver.17.1 Incidence % (n)

In randomized Japanese subjects who received study drug (21 subjects), the incidences of adverse events through Week 44 or up to the time of dose adjustment were 100.0% (4 of 4 subjects) in the placebo group, 100.0% (8 of 8 subjects) in the ustekinumab 90 mg/q12w group, and 88.9% (8 of 9 subjects) in the ustekinumab 90 mg/q8w group. No adverse drug reactions occurred in the placebo or ustekinumab 90 mg/q12w group, and the incidence of adverse drug reactions was 55.6% (5 of 9 subjects) in the ustekinumab 90 mg/q8w group. In randomized Japanese subjects who received study drug, adverse events reported by ≥2 subjects in any group through Week 44 or up to the time of dose adjustment are shown in Table 21, and the adverse drug reaction reported by ≥2 subjects in any group was nasopharyngitis (22.2% [2 of 9 subjects] in the ustekinumab 90 mg/q8w group).

Table 21. Adverse events reported by ≥2 subjects in any group (Randomized Japanese subjects who received study drug) [through Week 44 or up to time of dose adjustment]

	Maintenance phase (Subcutaneous injections)		
	Placebo (N = 4)	Ustekinumab	
		90 mg/q12w (N = 8)	90 mg/q8w (N = 9)
Any adverse event	100.0 (4)	100.0 (8)	88.9 (8)
Nasopharyngitis	25.0 (1)	25.0 (2)	44.4 (4)
Vulvovaginal candidiasis	0 (0)	0 (0)	22.2 (2)
Headache	0 (0)	37.5 (3)	11.1 (1)
Anal abscess	0 (0)	25.0 (2)	0 (0)

MedDRA ver.17.1 Incidence % (n)

In all randomized subjects who received study drug, no deaths occurred.

In all randomized subjects who received study drug, the incidences of serious adverse events through Week 44 or up to the time of dose adjustment were 15.0% (20 of 133 subjects) in the placebo group, 12.1% (16 of 132 subjects) in the ustekinumab 90 mg/q12w group, and 9.9% (13 of 131 subjects) in the ustekinumab 90 mg/q8w group, but no specific events tended to occur more frequently, except for the primary disease, Crohn's disease (Table 22). The incidences of serious adverse drug reactions were 1.5% (2 of 133 subjects) in the placebo group (Crohn's disease; and pneumonia, 1 subject each), 1.5% (2 of 132 subjects) in the ustekinumab 90 mg/q12w group (abdominal infection; and small intestinal obstruction, 1 subject each), and 2.3% (3 of 131 subjects) in the ustekinumab 90 mg/q8w group (viral infection; pneumonia; and ophthalmic herpes zoster, 1 subject each), and all those events resolved except for 1 case of abdominal infection (unresolved).

Table 22. Serious adverse events reported by ≥2 subjects in any group (All randomized subjects who received study drug) [through Week 44 or up to time of dose adjustment]

	Maintenance phase (Subcutaneous injections)		
	Placebo (N = 133)	Ustekinumab	
		90 mg/q12w (N = 132)	90 mg/q8w (N = 131)
Any serious adverse event	15.0 (20)	12.1 (16)	9.9 (13)
Crohn's disease	5.3 (7)	3.8 (5)	3.1 (4)
Large intestinal stenosis	0 (0)	0 (0)	1.5 (2)
Pneumonia	1.5 (2)	0 (0)	0.8 (1)
Appendicitis	0 (0)	1.5 (2)	0 (0)
Anal fistula	1.5 (2)	0 (0)	0 (0)

MedDRA ver.17.1 Incidence % (n)

In all randomized subjects who received study drug, the incidences of adverse events leading to discontinuation through Week 44 or up to the time of dose adjustment were 6.0% (8 of 133 subjects) in the placebo group, 7.6% (10 of 132 subjects) in the ustekinumab 90 mg/q12w group, and 3.1% (4 of 131 subjects) in the ustekinumab 90 mg/q8w group, and no specific events tended to occur more frequently, except for the primary disease, Crohn's disease (Table 23). Adverse drug reactions leading to discontinuation occurred in 0.8% (1 of 133) of subjects in the placebo group (tuberculosis) and 3.0% (4 of 132) of subjects in the ustekinumab 90 mg/q12w group (thyroiditis; Crohn's disease, large intestinal stenosis, and abdominal infection; rash; and furuncle, 1 subject each), and the events of thyroiditis, rash, and tuberculosis resolved, and Crohn's disease, large intestinal stenosis, and abdominal infection; and furuncle remained unresolved.

Table 23. Adverse events leading to discontinuation reported by ≥2 subjects in any group (All randomized subjects who received study drug) [through Week 44 or up to time of dose adjustment]

	Maintenance phase (Subcutaneous injections)		
	Placebo (N = 133)	Ustekinumab	
		90 mg/q12w (N = 132)	90 mg/q8w (N = 131)
Any adverse event leading to discontinuation	6.0 (8)	7.6 (10)	3.1 (4)
Pregnancy	0.8 (1)	0.8 (1)	1.5 (2)
Crohn's disease	2.3 (3)	2.3 (3)	0.8 (1)

MedDRA ver.17.1 Incidence % (n)

In randomized Japanese subjects who received study drug, no serious adverse events occurred through Week 44 or up to the time of dose adjustment in the placebo group, and the incidences of serious adverse events were 25.0% (2 of 8 subjects) in the ustekinumab 90 mg/q12w group (appendicitis and bacteraemia; and anal abscess) and 11.1% (1 of 9 subjects) in the ustekinumab 90 mg/q8w group (large intestinal obstruction). No serious adverse drug reactions occurred.

In randomized Japanese subjects who received study drug, 12.5% (1 of 8) of subjects in the ustekinumab 90 mg/q12w group experienced an adverse event leading to discontinuation (anal abscess) through Week 44 or up to the time of dose adjustment, but its causal relationship to study drug was ruled out.

In all randomized and non-randomized subjects who received study drug (all subjects who received study drug), the incidences of adverse events and adverse drug reactions through Week 44 are shown in Table 24 and Table 25, respectively.

Table 24. Adverse events reported by ≥3% of subjects in either group (All subjects who received study drug) [through Week 44]

	Induction phase + Maintenance phase			Induction phase + Maintenance phase	
	Placebo (N = 242)[a)]	Ustekinumab (N = 1157)[b)]		Placebo (N = 242)[a)]	Ustekinumab (N = 1157)[b)]
Any adverse event	81.8 (198)	75.1 (869)	Diarrhoea	6.6 (16)	3.9 (45)
Crohn's disease	14.0 (34)	13.0 (150)	Rash	3.3 (8)	3.9 (45)
Arthralgia	16.1 (39)	11.5 (133)	Sinusitis	2.9 (7)	3.8 (44)
Nasopharyngitis	9.1 (22)	10.7 (124)	Back pain	2.9 (7)	3.8 (44)
Headache	9.5 (23)	9.7 (112)	Gastroenteritis	3.3 (8)	3.2 (37)
Abdominal pain	10.7 (26)	8.6 (99)	Urinary tract infection	3.7 (9)	3.2 (37)
Upper respiratory tract infection	9.5 (23)	7.7 (89)	Influenza	2.9 (7)	3.1 (36)
Nausea	7.9 (19)	7.3 (85)	Abdominal pain upper	3.3 (8)	2.9 (33)
Pyrexia	8.3 (20)	6.0 (69)	Nasal congestion	3.7 (9)	1.4 (16)
Vomiting	5.4 (13)	4.8 (56)	Arthritis	3.7 (9)	1.3 (15)
Fatigue	4.5 (11)	4.1 (47)	Influenza like illness	3.7 (9)	1.2 (14)
Cough	3.7 (9)	4.1 (48)	Anal abscess	3.3 (8)	1.2 (14)

MedDRA ver.17.1 Incidence % (n)

a) Patients who received placebo in Study 3003 (Include data from Week 8 onward of Study 3003 for patients who were in CR to single intravenous infusion of ustekinumab in Study 3001 or 3002 and were randomized to the placebo group in Study 3003)

b) Patients who received ustekinumab in Study 3003 (Include data from Week 0 to Week 8 of Study 3003 for patients who were in CR to single intravenous infusion of ustekinumab in Study 3001 or 3002 and were randomized to the placebo group in Study 3003)

Table 25. Adverse drug reactions reported by ≥3% of subjects in either group (All subjects who received study drug) [through Week 44]

	Induction phase + Maintenance phase	
	Placebo (N = 242)[a)]	Ustekinumab (N = 1157)[b)]
Any adverse drug reaction	27.7 (67)	27.5 (318)
Headache	2.5 (6)	3.2 (37)
Upper respiratory tract infection	3.3 (8)	2.9 (33)
Nausea	3.3 (8)	1.7 (20)
Arthralgia	4.5 (11)	1.5 (17)

MedDRA ver.17.1 Incidence % (n)

a) Patients who received placebo in Study 3003 (Include data from Week 8 onward of Study 3003 for patients who were in CR to single intravenous infusion of ustekinumab in Study 3001 or 3002 and were randomized to the placebo group in Study 3003)

b) Patients who received ustekinumab in Study 3003 (Include data from Week 0 to Week 8 of Study 3003 for patients who were in CR to single intravenous infusion of ustekinumab in Study 3001 or 3002 and were randomized to the placebo group in Study 3003)

In all subjects who received study drug, no deaths occurred through Week 44.

In all subjects who received study drug, the incidences of serious adverse events through Week 44 were 15.3% (37 of 242 subjects) in the placebo-treated group and 14.7% (170 of 1157 subjects) in the ustekinumab-treated group. Serious adverse events reported by ≥3% of subjects in either group were Crohn's disease (4.5% [11 of 242] of placebo-treated subjects, 5.5% [64 of 1157] of ustekinumab-treated subjects). No specific events tended to occur more frequently, except for the primary disease, Crohn's disease and Crohn's disease-related events. In all subjects who received study drug, the incidences of serious adverse drug reactions through Week 44 were 0.8% (2 of 242 subjects) in the placebo-treated group and 1.6% (18 of 1157 subjects) in the ustekinumab-treated group. No serious adverse drug reactions were reported by ≥3% of subjects in either group.

In all subjects who received study drug, the incidences of adverse events leading to discontinuation through Week 44 were 6.2% (15 of 242 subjects) in the placebo-treated group and 5.1% (59 of 1157 subjects) in the ustekinumab-treated group. None of those events were reported by ≥3% of subjects in either group. No specific events tended to occur more frequently, except for the primary disease, Crohn's disease and Crohn's disease-

related events. In all subjects who received study drug, the incidences of adverse drug reactions leading to discontinuation through Week 44 were 1.7% (4 of 242 subjects) in the placebo-treated group and 1.0% (12 of 1157 subjects) in the ustekinumab-treated group. No adverse drug reactions leading to discontinuation were reported by ≥3% of subjects in either group.

In all randomized and non-randomized Japanese subjects who received study drug (all Japanese subjects who received study drug), the occurrence of adverse events through Week 44 is shown in Table 26. As to the occurrence of adverse drug reactions through Week 44 in all Japanese subjects who received study drug, adverse drug reactions reported by ≥2 subjects in either group were nasopharyngitis (0% [0 of 8 subjects] in the placebo-treated group, 4.3% [3 of 70 subjects] in the ustekinumab-treated group).

Table 26. Adverse events reported by ≥2 subjects in either group (All Japanese subjects who received study drug) [through Week 44]

	Induction phase + Maintenance phase			Induction phase + Maintenance phase	
	Placebo (N = 8)[a)]	Ustekinumab (N = 70)[b)]		Placebo (N = 8)[a)]	Ustekinumab (N = 70)[b)]
Any adverse event	87.5 (7)	80.0 (56)	Influenza	0 (0)	4.3 (3)
Nasopharyngitis	25.0 (2)	40.0 (28)	Pharyngitis	0 (0)	4.3 (3)
Crohn's disease	12.5 (1)	12.9 (9)	Abdominal pain upper	0 (0)	2.9 (2)
Headache	0 (0)	8.6 (6)	Anal fistula	0 (0)	2.9 (2)
Anal abscess	12.5 (1)	7.1 (5)	Anal stenosis	0 (0)	2.9 (2)
Dehydration	0 (0)	7.1 (5)	Arthralgia	12.5 (1)	2.9 (2)
Pyrexia	0 (0)	7.1 (5)	Contusion	0 (0)	2.9 (2)
Anaemia	0 (0)	5.7 (4)	Gastroenteritis	0 (0)	2.9 (2)
Back pain	0 (0)	5.7 (4)	Iron deficiency anaemia	12.5 (1)	2.9 (2)
Cough	0 (0)	5.7 (4)	Urticaria	0 (0)	2.9 (2)
Dental caries	0 (0)	5.7 (4)	Vomiting	0 (0)	2.9 (2)
Gastroenteritis viral	0 (0)	4.3 (3)	Vulvovaginal candidiasis	0 (0)	2.9 (2)

MedDRA ver.17.1 Incidence % (n)

a) Patients who received placebo in Study 3003 (Include data from Week 8 onward of Study 3003 for patients who were in CR to single intravenous infusion of ustekinumab in Study 3001 or 3002 and were randomized to the placebo group in Study 3003)

b) Patients who received ustekinumab in Study 3003 (Include data from Week 0 to Week 8 of Study 3003 for patients who were in CR to single intravenous infusion of ustekinumab in Study 3001 or 3002 and were randomized to the placebo group in Study 3003)

In all Japanese subjects who received study drug, no deaths occurred through Week 44. In all Japanese subjects who received study drug, the incidences of serious adverse events through Week 44 were 0% (0 of 8 subjects) in the placebo-treated group and 24.3% (17 of 70 subjects) in the ustekinumab-treated group. Serious adverse events reported by ≥2 subjects in either group were Crohn's disease (0% [0 of 8 subjects] in the placebo-treated group, 12.9% [9 of 70 subjects] in the ustekinumab-treated group) and anal abscess (0% [0 of 8 subjects] in the placebo-treated group, 2.9% [2 of 70 subjects] in the ustekinumab-treated group). No specific events tended to occur more frequently, except for the primary disease, Crohn's disease and Crohn's disease-related events. In all Japanese subjects who received study drug, the incidences of serious adverse drug reactions through Week 44 were 0% (0 of 8 subjects) in the placebo-treated subjects and 1.4% (1 of 70 subjects) in the ustekinumab-treated group, and no serious adverse drug reactions were reported by ≥2 subjects in either group.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package including data from global studies

Studies 3001, 3002, and 3003, which were submitted in this application as evaluation data, were all global studies. The applicant's explanation of intrinsic and extrinsic ethnic differences between Japan and the major participating countries, the EU/US:

As to intrinsic ethnic factors, ustekinumab is a monoclonal antibody, and it was considered that there should be little racial differences in its metabolism and excretion. Studies 3001, 3002, and 3003 showed no major pharmacokinetic differences between non-Japanese and Japanese subjects [see Section 6.2].

As to extrinsic ethnic factors, the diagnostic criteria for CD are largely similar between Japan and the EU/US. With regard to treatments selected according to disease activity, i.e. during the active and maintenance phases, though enteral nutritional therapy tends to be used commonly in Japan compared to the EU/US, as there were restrictions regarding its use in Studies 3001, 3002, and 3003, it was considered that there would be no major differences compared to the EU/US, where drug therapy is the mainstay. CDAI is widely used worldwide to measure the activity of CD, and there should be no problem with efficacy assessment of ustekinumab using the CDAI tool.

Based on the above, it was considered that there should be no problem with participation of Japan in the global studies. There are a limited number of patients with CD, and the number of patients with CD in Japan at the time of planning the studies[7)] was estimated at about 30,000, based on the number of recipient certificates issued for specific disease treatment for patients with CD. In Japan, the number of patients who had failed or were intolerant to anti-TNF therapy, i.e. the study population for Study 3001, was estimated at about 500 to 5600, based on the results of post-marketing surveillance of similar drugs and publications (Interim report on use-results survey of Remicade for intravenous infusion 100, *THE LANCET*. 2002; 359: 1541-49) etc. Also, with a view to feasibility, a target sample size of 60 subjects was chosen for Study 3001. It was considered that patient enrollment in Study 3002 would be more difficult and smaller because anti-TNF agents are widely used in Japan. Based on these considerations and taking account of the feasibility of enrollment within the period of each global study, target sample sizes of 60 Japanese subjects for Study 3001 and 20 Japanese subjects for Study 3002 were chosen.

PMDA's view:

Given the situation (the number of patients with CD, etc.) in Japan at the time of planning the studies, it was inevitable that there was a limitation on the number of patients that could be enrolled within the period of each global study. There is no particular problem with participation of Japan in the global studies. Though the number of Japanese patients was limited, taking also account of the situation at the time of planning the studies, the efficacy and safety of ustekinumab may be assessed based on the results of Studies 3001, 3002, and 3003 involving Japan.

[7)] Fiscal year 2009

7.R.2 Efficacy

PMDA's view:

Based on the considerations in 7.R.2.1 and 7.R.2.2, the efficacy of ustekinumab induction and maintenance therapy in patients with moderately to severely active CD who have had an inadequate response to conventional therapy has been demonstrated.

A final conclusion on the efficacy of ustekinumab will be made, taking account of comments from the Expert Discussion.

7.R.2.1 Induction phase

7.R.2.1.1 Efficacy of ustekinumab induction therapy for CD

The applicant's explanation of the efficacy of ustekinumab induction therapy for CD:

The efficacy of ustekinumab induction therapy for CD was evaluated in Studies 3001 and 3002 in patients with moderately to severely active CD who had failed existing therapy. Since an on-site GCP inspection revealed an error in data entry (baseline CDAI score) for 1 Japanese subject in Study 3001 (ustekinumab 6 mg/kg group), an analysis using a corrected CDAI score was also performed for the following evaluation (the analysis using a corrected CDAI score).

Both Studies 3001 and 3002 demonstrated the superiority of each dose of ustekinumab over placebo in the primary endpoint of the CR rate at Week 6 in the entire study population (Table 6 and Table 13). The analysis using a corrected CDAI score also produced results not substantially different from the efficacy results in the entire study population of Study 3001 (Table 27). The results of the primary endpoint (CR rate at Week 6) in the Japanese population of Study 3001 or 3002 are shown in Table 28. The results in the Japanese population of Study 3001 showed that the CR rate at Week 6 was similar between the ustekinumab 6 mg/kg and placebo groups. The results in the Japanese population of Study 3002 showed that the CR rate at Week 6 tended to be higher in each ustekinumab group than in the placebo group.

Table 27. CR rate at Week 6 in the entire study population of Study 3001 or 3002

	Induction phase (Single intravenous infusion)					
	Study 3001[a)]			Study 3002		
	Placebo	Ustekinumab		Placebo	Ustekinumab	
		130 mg	6 mg/kg		130 mg	6 mg/kg
N	247	245	249	209	209	209
CR rate	21.5 (53)	34.3 (84)	33.3 (83)	28.7 (60)	51.7 (108)	55.5 (116)
Difference from placebo [95% CI]	—	12.8 [5.0, 20.7]	11.9 [4.1, 19.7]	—	23.0 [13.8, 32.1]	26.8 [17.7, 35.9]

Proportion % (n)

a) Analysis using a corrected CDAI score

Table 28. CR rate at Week 6 in the Japanese population of Study 3001 or 3002

	Induction phase (Single intravenous infusion)					
	Study 3001 [a)]			Study 3002		
	Placebo	Ustekinumab		Placebo	Ustekinumab	
		130 mg	6 mg/kg		130 mg	6 mg/kg
N	18	19	19	9	8	9
CR rate	27.8 (5)	36.8 (7)	26.3 (5)	11.1 (1)	37.5 (3)	55.6 (5)
Difference from placebo [95% CI]	—	9.1 [-20.9, 39.0]	-1.5 [-30.1, 27.2]	—	26.4 [-12.9, 65.7]	44.4 [6.0, 82.9]

Proportion % (n)
a) Analysis using a corrected CDAI score

As a possible reason that the treatment difference between the ustekinumab 6 mg/kg and placebo groups tended to be different between the Japanese and entire study populations of Study 3001, differences in patient characteristics were examined. Baseline values tended to be different between the entire and Japanese populations, mainly for body weight (69.8 ± 18.2 kg in the entire study population, 55.8 ± 9.7 kg in the Japanese population) and CRP (1.9 ± 2.4 mg/dL in the entire study population, 2.0 ± 2.4 mg/dL in the Japanese population) (mean ± SD), which may have affected the results. However, no definitive conclusion could be made due to the limited number of Japanese subjects.

Though it was a secondary endpoint, the clinical remission rates at Week 8 in the entire and Japanese populations of Study 3001 or 3002 are shown in Table 29 and Table 30, respectively, and both Studies 3001 and 3002 showed no major differences between the entire and Japanese populations for the treatment difference between each ustekinumab and placebo groups.

Table 29. Clinical remission rate at Week 8 (Entire study population of Study 3001 or 3002)

	Induction phase (Single intravenous infusion)					
	Study 3001 [a)]			Study 3002		
	Placebo	Ustekinumab		Placebo	Ustekinumab	
		130 mg	6 mg/kg		130 mg	6 mg/kg
N	247	245	249	209	209	209
Clinical remission rate	7.3 (18)	15.9 (39)	20.9 (52)	19.6 (41)	30.6 (64)	40.2 (84)
Difference from placebo [95% CI]	—	8.6 [3.0, 14.2]	13.6 [7.6, 19.6]	—	11.0 [2.8, 19.3]	20.6 [12.0, 29.1]

Proportion % (n)
a) Analysis using a corrected CDAI score

Table 30. Clinical remission rate at Week 8 (Japanese population of Study 3001 or 3002)

	Induction phase (Single intravenous infusion)					
	Study 3001 [a)]			Study 3002		
	Placebo	Ustekinumab		Placebo	Ustekinumab	
		130 mg	6 mg/kg		130 mg	6 mg/kg
N	18	19	19	9	8	9
Clinical remission rate	5.6 (1)	10.5 (2)	26.3 (5)	0 (0)	25.0 (2)	22.2 (2)
Difference from placebo [95% CI]	—	5.0 [-12.4, 22.4]	20.8 [-1.7, 43.2]	—	25.0 [-5.0, 55.0]	22.2 [-4.9, 49.4]

Proportion % (n)
a) Analysis using a corrected CDAI score

Based on the above, the results in the entire study population of Studies 3001 and 3002 demonstrated the efficacy of ustekinumab in patients with active CD who had failed existing therapy, and the efficacy of ustekinumab in the Japanese population is also expected.

PMDA's view, taking account of 7.R.2.1.1 and 7.R.2.1.2:
Both Studies 3001 and 3002 demonstrated the superiority of 130 mg and 6 mg/kg of ustekinumab over placebo in the primary endpoint of the CR rate at Week 6 in the entire study population (Table 6 and Table 13), and the analysis using a corrected CDAI score also found no particular efficacy issues in the entire study population (Table 27). Based on the above, the efficacy of ustekinumab induction therapy in the entire study population of patients with moderately to severely active CD who had failed existing therapy was demonstrated.

Regarding efficacy in the Japanese population, the primary endpoint of the CR rate at Week 6 (the analysis using a corrected CDAI score) tended to be higher in the ustekinumab 130 mg group than in the placebo group, but was similar between the ustekinumab 6 mg/kg and placebo groups in Study 3001. Though the reason for a similar CR rate at Week 6 between the ustekinumab 6 mg/kg and placebo groups in the Japanese population of Study 3001 is unknown, the limited number of Japanese subjects may have affected the results. On the other hand, in Study 3002, there was no problematic trend in the treatment difference in the CR rate at Week 6 (the primary endpoint) between each ustekinumab and placebo groups in the Japanese population, compared with the entire study population. Though it was a secondary endpoint, both Studies 3001 and 3002 showed no trend towards a smaller treatment difference in the clinical remission rate at Week 8 between each ustekinumab and placebo groups in the Japanese population compared with the entire study population (Table 29 and Table 30). Based on the above, the efficacy of ustekinumab induction therapy is expected also in Japanese patients with moderately to severely active CD who have failed existing therapy.

However, due to the limited number of Japanese subjects in Studies 3001 and 3002, it is necessary to collect information on the efficacy of ustekinumab in Japanese patients with CD via post-marketing surveillance etc.

7.R.2.1.2 Efficacy by response to anti-TNF therapy

The applicant's explanation of the efficacy of ustekinumab by response to anti-TNF therapy, based on the results of Study 3001:
Study 3001 enrolled patients who had received anti-TNF therapy (infliximab, adalimumab, or certolizumab pegol), and did not respond initially (primary non-response), responded initially but then lost response (secondary non-response), or were intolerant to the medication. As the treatment response to ustekinumab may differ by response to anti-TNF therapy, the efficacy of ustekinumab by response to anti-TNF therapy was investigated.

The CR rate at Week 6 by response to anti-TNF therapy in Study 3001 is shown in Table 31. In the entire study population, the CR rate tended to be higher in each ustekinumab group than in the placebo group among secondary non-responders or intolerant patients. On the other hand, the CR rate in each ustekinumab group was similar to that in the placebo group among primary non-responders, which may have been due to the insufficient sample size. No restrictions regarding the use of ustekinumab in primary non-responders to anti-TNF therapy are specified in the US/EU labeling.

Table 31. CR rate at Week 6 by response to anti-TNF therapy (Study 3001)[a)]

	Induction phase (Single intravenous infusion)					
	Entire study population			Japanese population		
	Placebo (N = 247)	Ustekinumab		Placebo (N = 18)	Ustekinumab	
		130 mg (N = 245)	6 mg/kg (N = 249)		130 mg (N = 19)	6 mg/kg (N = 19)
Primary non-response						
N	74	70	72	0	1	0
CR rate	23.0 (17)	28.6 (20)	23.6 (17)	—	0 (0)	—
Secondary non-response						
N	170	173	171	18	18	18
CR rate	20.0 (34)	31.8 (55)	36.3 (62)	27.8 (5)	33.3 (6)	22.2 (4)
Intolerant						
N	87	78	105	2	1	3
CR rate	24.1 (21)	38.5 (30)	34.3 (36)	0 (0)	100 (1)	33.3 (1)

Proportion % (n)
a) Analysis using a corrected CDAI score

PMDA's view:

Table 31 shows no particularly problematic trend in the efficacy of each dose of ustekinumab compared to placebo in secondary non-responders to anti-TNF therapy or intolerant patients in the entire study population. On the other hand, it is unknown at present whether the applicant's explanation (the results in primary non-responders may have been due to the small number of subjects in each group) is correct. It is necessary to collect information on the efficacy of ustekinumab by response to anti-TNF therapy via post-marketing surveillance etc.

7.R.2.1.3 Efficacy by prior therapy other than anti-TNF therapy

The applicant's explanation of the efficacy of ustekinumab by prior therapy other than anti-TNF therapy, based on the results of Study 3002:

Study 3002 enrolled patients who had failed conventional therapy (immunomodulators and/or corticosteroids [including patients who were corticosteroid-dependent]). Patients who had previously received anti-TNF therapy were eligible provided that they had not met the criteria for primary or secondary non-response and were not intolerant to the medication (patients ineligible for Study 3001).

The CR rate at Week 6 by concomitant medications at baseline in Study 3002 is shown in Table 32. Regardless of medications at baseline, the CR rate was higher with each dose of ustekinumab compared to placebo.

Table 32. CR rate at Week 6 by conventional therapy (Study 3002)

	Induction phase (Single intravenous infusion)					
	Entire study population			Japanese population		
	Placebo (N = 209)	Ustekinumab		Placebo (N = 9)	Ustekinumab	
		130 mg (N = 209)	6 mg/kg (N = 209)		130 mg (N = 8)	6 mg/kg (N = 9)
5-ASA						
Yes	29.2 (26/89)	48.3 (43/89)	60.2 (56/93)	14.3 (1/7)	28.6 (2/7)	42.9 (3/7)
No	28.3 (34/120)	54.2 (65/120)	51.7 (60/116)	0.0 (0/2)	100.0 (1/1)	100.0 (2/2)
Corticosteroids						
Yes	34.7 (26/75)	48.8 (39/80)	56.5 (52/92)	0.0 (0/2)	— (0/0)	0 (0/1)
No	25.4 (34/134)	53.5 (69/129)	54.7 (64/117)	14.3 (1/7)	37.5 (3/8)	62.5 (5/8)
6-MP/AZA/MTX						
Yes	28.8 (21/73)	58.1 (43/74)	65.3 (47/72)	0 (0/3)	33.3 (1/3)	100.0 (4/4)
No	28.7 (39/136)	48.1 (65/135)	50.4 (69/137)	16.7 (1/6)	40.0 (2/5)	20.0 (1/5)

Proportion % (n/N)

PMDA considers that at present, there is no particularly problematic trend in the efficacy of ustekinumab by prior therapy other than anti-TNF therapy.

7.R.2.1.4 Efficacy by disease activity measured by baseline CDAI score

The applicant's explanation of the efficacy of ustekinumab by disease activity measured by baseline CDAI score:

The CR rates at Week 6 by disease activity measured by baseline CDAI score in Studies 3001 and 3002 are shown in Table 33. In the entire study population, the CR rate at Week 6 was higher with 130 mg or 6 mg/kg of ustekinumab compared to placebo in both the baseline CDAI score ≤300 and >300 subgroups.

Table 33. CR rate at Week 6 by baseline CDAI score (Studies 3001 and 3002)

Study	Baseline CDAI	Induction phase (Single intravenous infusion)					
		Entire study population			Japanese population		
		Placebo	Ustekinumab		Placebo	Ustekinumab	
			130 mg	6 mg/kg		130 mg	6 mg/kg
3001[a)]	≤ 300	17.3 (18/104)	32.7 (33/101)	28.4 (27/95)	10.0 (1/10)	25.0 (2/8)	30.0 (3/10)
	> 300	24.5 (35/143)	35.4 (51/144)	36.4 (56/154)	50.0 (4/8)	45.5 (5/11)	22.2 (2/9)
3002	≤ 300	24.4 (30/123)	39.8 (45/113)	51.3 (61/119)	14.3 (1/7)	33.3 (2/6)	50.0 (3/6)
	> 300	34.9 (30/86)	65.6 (63/96)	61.1 (55/90)	0.0 (0/2)	50.0 (1/2)	66.7 (2/3)

Proportion % (n/N)
a) Analysis using a corrected CDAI score

PMDA considers that at present, there is no particularly problematic trend in the efficacy of ustekinumab by disease activity measured by baseline CDAI score in the entire study population.

7.R.2.2 Maintenance phase

7.R.2.2.1 Efficacy of ustekinumab maintenance therapy for CD

The applicant's explanation of the efficacy of ustekinumab maintenance therapy for CD:

The efficacy of ustekinumab maintenance therapy for CD was evaluated in Study 3003. An on-site GCP inspection revealed an error in data entry (baseline CDAI score) for 1 Japanese subject in Study 3001. Based on the wrong baseline CDAI score, this subject was randomized as a responder in Study 3001 to the ustekinumab 90 mg/q8w group in Study 3003. However, based on the correct baseline CDAI score, this subject was not a responder in Study 3001, and should not have been included in the primary analysis population of Study 3003. Thus, an analysis excluding this subject was also performed (the analysis using a corrected CDAI score).

Study 3003 demonstrated the superiority of ustekinumab 90 mg/q12w and 90 mg/q8w over placebo in the primary endpoint of the clinical remission rate at Week 44 in the entire study population (Table 18). The analysis using a corrected CDAI score also produced results not substantially different from the efficacy results in the entire study population of Study 3003 (Table 34). Though the number of Japanese subjects in the primary analysis population of Study 3003 was limited, there were no major differences in the results between the Japanese and entire study populations (Table 34).

Table 34. Clinical remission rate at Week 44 in the entire and Japanese populations of Study 3003 (Primary analysis population)[a)]

	Maintenance phase (Subcutaneous injections)					
	Entire study population			Japanese population		
	Placebo	Ustekinumab		Placebo	Ustekinumab	
		90 mg/q12w	90 mg/q8w		90 mg/q12w	90 mg/q8w
N	131	129	127	4	8	8
Clinical remission rate (n)	35.9 (47)	48.8 (63)	53.5 (68)	25.0 (1)	50.0 (4)	62.5 (5)
Difference from placebo [95% CI]	—	13.0 [1.1, 24.9]	17.7 [5.7, 29.6]	—	25.0 [-29.8, 79.8]	37.5 [-16.6, 91.6]

Proportion % (n)
a) Analysis using a corrected CDAI score

PMDA's view:

Since ustekinumab 90 mg/q12w and 90 mg/q8w were shown to be superior over placebo in the primary endpoint of the clinical remission rate at Week 44 in the entire study population, the efficacy of ustekinumab maintenance therapy was demonstrated.

Regarding the efficacy of ustekinumab in the Japanese population, though it should be noted that the number of Japanese subjects was limited, there were no major differences in efficacy trend between the entire and Japanese populations. No particular differences in the efficacy results were observed between analyses including and excluding the Japanese subject with an error in data entry (baseline CDAI score). However, as the number of Japanese subjects in Study 3003 was limited, it is necessary to collect information on the efficacy of ustekinumab maintenance therapy in Japanese patients with CD via post-marketing surveillance etc.

7.R.2.2.2 CDAI score over time

The applicant's explanation of the CDAI score over time in Study 3003:

The mean CDAI score over time in Study 3003 is shown in Figure 7. While the mean score tended to increase over time in the placebo group, the mean score was maintained up to Week 44 in the ustekinumab 90 mg/q12w and 90 mg/q8w groups.

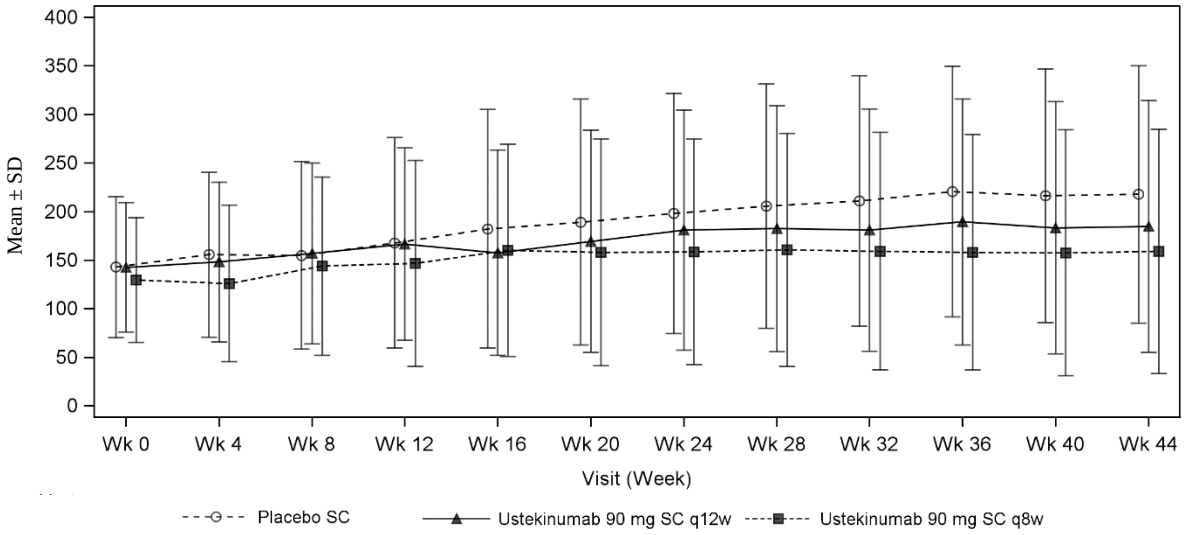


Figure 7. CDAI score over time in Study 3003 (Primacy analysis population, LOCF)
※Analysis using a corrected CDAI score

PMDA considers that at present, there is no particularly problematic trend in the CDAI score over time in each ustekinumab group in Study 3003.

7.R.2.2.3 Withdrawal of corticosteroids

The applicant's explanation of the withdrawal of corticosteroids after treatment with ustekinumab:

In the primary analysis population of Study 3003, 45.7% (181 of 396) of subjects were receiving corticosteroids at baseline (44.4% [59 of 133 subjects] in the placebo group, 43.9% [58 of 132 subjects] in the ustekinumab 90 mg/q12w group, 48.9% [64 of 131 subjects] in the ustekinumab 90 mg/q8w group). Among those subjects receiving corticosteroids, the corticosteroid-free clinical remission rates at Week 44 were 15.5% (9 of 58 subjects) in the placebo group, 29.8% (17 of 57 subjects) in the ustekinumab 90 mg/q12w group, and 30.5% (18 of 59 subjects) in the ustekinumab 90 mg/q8w group, suggesting a trend towards a higher rate in the 90 mg/q12w and 90 mg/q8w groups compared to the placebo group.[8)]

PMDA considers that there is no particular problem with the applicant's explanation.

7.R.3 Safety

PMDA decided to evaluate the safety of ustekinumab based primarily on the results of the randomized populations in Studies 3001, 3002, and 3003. PMDA also referred to the results of the non-randomized population and pooled data from multiple studies for the evaluation of the long-term safety, significant adverse events with a low incidence, etc.

Based on the considerations in 7.R.3.1 to 7.R.3.5, PMDA considers that the safety of ustekinumab is acceptable as long as appropriate precautions are provided, in accordance with the package insert for the approved indications of psoriasis vulgaris and psoriatic arthritis. However, as the number of Japanese CD patients treated with ustekinumab was limited, it is necessary to further collect ustekinumab safety information via post-marketing surveillance etc.

A final conclusion on the safety of ustekinumab will be made, taking account of comments from the Expert Discussion.

7.R.3.1 Comparison with placebo

The applicant's explanation of a summary of the safety of ustekinumab compared to placebo:

Since with the exception of previous TNF antagonist experience, Studies 3001 and 3002 were identical in design, these 2 studies were pooled, and the safety of ustekinumab in patients with active disease was evaluated using the data from all subjects who received study drug (including subjects enrolled prior to the study interruption). A summary of adverse events is shown in Table 35, and there were no major differences between the placebo group and the ustekinumab 130 mg or 6 mg/kg group. The incidence of adverse events leading to treatment discontinuation tended to be higher in the placebo group. A similar trend was observed also in the Japanese population.

[8)] Analysis using a corrected CDAI score

Table 35. Summary of adverse events through Week 8 (Pooled analysis of Studies 3001 and 3002)

	Induction phase (Single intravenous infusion)					
	Entire study population			Japanese population		
	Placebo	Ustekinumab		Placebo	Ustekinumab	
		130 mg	6 mg/kg		130 mg	6 mg/kg
N	466	471	470	27	27	28
All adverse events	60.5 (282)	58.4 (275)	60.4 (284)	55.6 (15)	44.4 (12)	50.0 (14)
All adverse drug reactions	22.5 (105)	19.5 (92)	20.4 (96)	18.5 (5)	11.1 (3)	10.7 (3)
Serious adverse events	6.0 (28)	4.9 (23)	5.3 (25)	7.4 (2)	0 (0)	7.1 (2)
Adverse events leading to discontinuation	4.1 (19)	1.7 (8)	1.7 (8)	3.7 (1)	0 (0)	0 (0)
Infections	23.2 (108)	19.5 (92)	23.6 (111)	22.2 (6)	18.5 (5)	25.0 (7)
Serious infections	1.3 (6)	1.5 (7)	1.7 (8)	0 (0)	0 (0)	0 (0)
Infusion reactions	2.4 (11)	3.6 (17)	2.6 (12)	3.7 (1)	0 (0)	0 (0)

Incidence % (n)

The safety of ustekinumab during the maintenance phase after Week 8 of the induction studies was evaluated using the data from randomized subjects who received study drug in Study 3003. A summary of adverse events through Week 44 (52 weeks from the initiation of the induction dose) or up to the time of dose adjustment [see Figure 5 and Figure 6] is shown in Table 36, and there were no major differences between the placebo group and the ustekinumab 90 mg/q12w or 90 mg/q8w group. In the Japanese population, although the incidence of adverse drug reactions tended to be higher in the ustekinumab 90 mg/q8w group, only nasopharyngitis (22.2% [2 of 9 subjects] in the ustekinumab 90 mg/q8w group) was reported by ≥2 subjects. The incidence of infections tended to be higher in the ustekinumab 90 mg/q8w group, and nasopharyngitis was commonly reported [see Section 7.R.3.3.1].

Table 36. Summary of adverse events through Week 44 or up to the time of dose adjustment (Study 3003; Randomized subjects who received study drug)

	Maintenance phase (Subcutaneous injections)					
	Entire study population			Japanese population		
	Placebo	Ustekinumab		Placebo	Ustekinumab	
		90 mg/q12w	90 mg/q8w		90 mg/q12w	90 mg/q8w
N	133	132	131	4	8	9
All adverse events	83.5 (111)	80.3 (106)	81.7 (107)	100.0 (4)	100.0 (8)	88.9 (8)
All adverse drug reactions	31.6 (42)	25.8 (34)	29.8 (39)	0 (0)	0 (0)	55.6 (5)
Serious adverse events	15.0 (20)	12.1 (16)	9.9 (13)	0 (0)	25.0 (2)	11.1 (1)
Adverse events leading to discontinuation	6.0 (8)	7.6 (10)	3.1 (4)	0 (0)	12.5 (1)	0 (0)
Infections	49.6 (66)	46.2 (61)	48.1 (63)	50.0 (2)	62.5 (5)	88.9 (8)
Serious infections	2.3 (3)	5.3 (7)	2.3 (3)	0 (0)	25.0 (2)	0 (0)

Incidence % (n)

With regard to adverse events through 52 weeks after the initiation of study drug administration in Studies 3001, 3002, and 3003, adverse events by time from the onset of therapy are shown in Table 37. No clear association between treatment duration and the occurrence of adverse events was observed in either the placebo- or ustekinumab-treated group, and there were no clinically relevant differences between the ustekinumab- and placebo-treated groups.

Table 37. Adverse events reported by ≥3% of subjects in either group by time from onset of therapy (Study 3001, Study 3002, Study 3003, Entire study population)

	Induction phase (Single intravenous infusion)		Maintenance phase (Multiple subcutaneous injections)					
	Study 3001/Study 3002		Study 3003					
No. of weeks[a)]	0-8 weeks		9-20 weeks[a)] (0-12 weeks)		21-32 weeks[a)] (13-24 weeks)		33-52 weeks[a)] (25-44 weeks)	
Group	Placebo[b)]	Ustekinumab[c)]	Placebo[d)]	Ustekinumab[e)]	Placebo[d)]	Ustekinumab[e)]	Placebo[d)]	Ustekinumab[e)]
N	466	941	123	1157	121	1056	112	832
Any adverse event	60.5 (282)	59.4 (559)	57.7 (71)	59.6 (690)	64.5 (78)	50.5 (533)	61.6 (69)	60.7 (505)
Crohn's disease	7.5 (35)	3.8 (36)	8.1 (10)	6.0 (69)	5.0 (6)	5.6 (59)	6.3 (7)	6.5 (54)
Nasopharyngitis	4.9 (23)	5.0 (47)	4.1 (5)	5.3 (61)	5.0 (6)	4.6 (49)	6.3 (7)	6.0 (50)
Arthralgia	4.7 (22)	6.4 (60)	7.3 (9)	6.5 (75)	9.1 (11)	4.1 (43)	9.8 (11)	5.9 (49)
Abdominal pain	4.3 (20)	4.0 (38)	3.3 (4)	4.3 (50)	5.0 (6)	2.6 (27)	4.5 (5)	5.3 (44)
Headache	7.9 (37)	7.5 (71)	5.7 (7)	5.4 (62)	6.6 (8)	3.0 (32)	1.8 (2)	4.9 (41)
Upper respiratory tract infection	4.3 (20)	3.6 (34)	2.4 (3)	3.6 (42)	0.8 (1)	3.2 (34)	3.6 (4)	4.2 (35)
Nausea	4.7 (22)	5.5 (52)	0.8 (1)	4.0 (46)	6.6 (8)	2.2 (23)	4.5 (5)	3.7 (31)
Pyrexia	5.4 (25)	5.1 (48)	5.7 (7)	3.3 (38)	3.3 (4)	2.3 (24)	5.4 (6)	3.2 (27)
Vomiting	2.6 (12)	3.6 (34)	0.8 (1)	2.0 (23)	0.8 (1)	2.5 (26)	2.7 (3)	3.0 (25)
Diarrhoea	2.1 (10)	0.7 (7)	2.4 (3)	1.1 (13)	1.7 (2)	1.9 (20)	4.5 (5)	2.2 (18)
Urinary tract infection	1.1 (5)	0.6 (6)	1.6 (2)	1.6 (19)	3.3 (4)	0.9 (9)	1.8 (2)	1.6 (13)
Abdominal pain upper	0.6 (3)	1.0 (9)	1.6 (2)	1.1 (13)	3.3 (4)	1.2 (13)	1.8 (2)	1.3 (11)
Fatigue	3.4 (16)	2.4 (23)	4.1 (5)	2.4 (28)	1.7 (2)	1.1 (12)	2.7 (3)	1.4 (12)
Arthritis	1.5 (7)	1.0 (9)	0.8 (1)	0.7 (8)	4.1 (5)	0.4 (4)	0.9 (1)	0.7 (6)
Anaemia	1.7 (8)	1.3 (12)	0.8 (1)	0.7 (8)	3.3 (4)	1.1 (12)	0.9 (1)	0.6 (5)
Anal abscess	1.3 (6)	0.6 (6)	0 (0)	0.7 (8)	3.3 (4)	0.5 (5)	1.8 (2)	0.6 (5)

Incidence % (n)

a) Number of weeks from the initiation of the induction dose in Study 3001 or 3002. Number of weeks from the first maintenance dose in Study 3003 in parenthesis.

b) Placebo group in Study 3001 or 3002

c) Ustekinumab 130 mg or 6 mg/kg group in Study 3001 or 3002

d) Subjects who received subcutaneous placebo only in Study 3003

e) Subjects who received ustekinumab in Study 3001 or 3002 and received ustekinumab also in Study 3003

PMDA's view:

Based on Table 35, Table 36, and Table 37, there were no relevant differences in the occurrence of adverse events between ustekinumab- and placebo-treated subjects in the entire study population. In the Japanese population, though the number of Japanese subjects was limited, there were no relevant differences between ustekinumab- and placebo-treated subjects.

7.R.3.2 Long-term safety

The applicant's explanation of deaths and serious adverse events during long-term treatment:

In Study 3003, subjects who completed the Week 44 (52 weeks from the initiation of the induction dose in Study 3001 or 3002) evaluation were allowed to enter the long-term extension phase[9)] continuing up to Week 272, in the judgment of the investigator.

In Study 3003, 605 subjects (including 41 Japanese subjects) continued to receive ustekinumab after Week 44 (a mean follow-up period of 68.8 weeks), and 6 deaths (cardio-respiratory arrest; renal failure chronic; acute myocardial infarction; sudden death; asphyxia (suicide); and septic shock) occurred between the Week 44 database lock and October 1, 2015. A causal relationship to study drug was ruled out for all those cases, and there were no deaths in Japanese subjects. The incidences of serious adverse events were 16.7% (101 of 605 subjects) in the entire study population and 29.3% (12 of 41 subjects) in the Japanese population. Serious adverse events reported by ≥1% of subjects in the entire study population were Crohn's disease (5.0% [30 of 605 subjects]), small intestinal obstruction (1.5% [9 of 605 subjects]), and anal abscess (1.3% [8 of 605 subjects]). In the Japanese population, Crohn's disease occurred in 4 subjects, small intestinal obstruction in 1 subject, and anal abscess in 1 subject. In addition, serious adverse events were reported by 68 subjects in the entire study population and 4 subjects in the Japanese population between October 1, 2015 and August 31, 2016. Those reported by ≥2 subjects in the entire study population were Crohn's disease (9 subjects), small intestinal obstruction (3 subjects), osteoarthritis (3 subjects), anal abscess (2 subjects), cellulitis (2 subjects), gastroenteritis (2 subjects), and perirectal abscess (2 subjects). No serious adverse events were reported by ≥2 subjects in the Japanese population.

PMDA's view:

Regarding long-term safety, no specific events tended to occur more frequently, except for the primary disease, Crohn's disease and Crohn's disease-related events, and there is no particularly problematic trend at present. Infections and malignancies will be discussed in 7.R.3.3.

7.R.3.3 Significant adverse events

The applicant's explanation of the occurrence of infections, infusion reactions and anaphylaxis, injection site reactions, malignancies, and serious neurological disease, which are listed as adverse events deserving special attention in the package insert for ustekinumab:

7.R.3.3.1 Infections

The applicant's explanation of the occurrence of infections in Studies 3001, 3002, and 3003:

All adverse events that were considered by the investigator to be infections, including but not limited to events in the MedDRA SOC "Infections and infestations," were collected and analyzed.

[9)] Subjects were to continue to receive the same treatment regimen that they were receiving at the end of the main study (through Week 44) (either placebo or 90 mg SC ustekinumab q8W or q12W), and there was to be no dose adjustment. The study blind was maintained in the study extension until the last subject in the main study completed the Week 44 evaluations and the Week 44 analyses had been completed. After the study was unblinded, patients receiving placebo were terminated from study participation.

The occurrence of serious infections through Week 8 (pooled analysis of Studies 3001 and 3002) in the entire study population is shown in Table 38. There were no major differences among the groups, and no specific events tended to occur more frequently. In the Japanese population, the incidences of infections were 22.2% (6 of 27 subjects) in the placebo group, 18.5% (5 of 27 subjects) in the ustekinumab 130 mg group, and 25.0% (7 of 28 subjects) in the ustekinumab 6 mg/kg group, and there were no major differences among the groups. No serious infections occurred in the Japanese population.

Table 38. Serious infections through Week 8 (Pooled analysis of Studies 3001 and 3002, Entire study population)

		Induction phase (Single intravenous infusion)		
		Placebo (N = 466)	Ustekinumab	
			130 mg (N = 471)	6 mg/kg (N = 470)
All infections		23.2 (108)	19.5 (92)	23.6 (111)
Serious infections		1.3 (6)	1.5 (7)	1.7 (8)
	Abscess intestinal	0 (0)	0.2 (1)	0.2 (1)
	Clostridium difficile infection	0 (0)	0 (0)	0.2 (1)
	Escherichia sepsis	0 (0)	0 (0)	0.2 (1)
	Gastroenteritis	0 (0)	0 (0)	0.2 (1)
	Intervertebral discitis	0 (0)	0 (0)	0.2 (1)
	Meningitis listeria	0 (0)	0 (0)	0.2 (1)
	Perineal abscess	0 (0)	0 (0)	0.2 (1)
	Peritonitis	0 (0)	0 (0)	0.2 (1)
	Cholangitis	0 (0)	0 (0)	0.2 (1)
	Anal abscess	0.4 (2)	0.4 (2)	0 (0)
	Gastroenteritis viral	0 (0)	0.2 (1)	0 (0)
	Pelvic abscess	0 (0)	0.2 (1)	0 (0)
	Vulval abscess	0 (0)	0.2 (1)	0 (0)
	Diarrhoea	0 (0)	0.2 (1)	0 (0)
	Infected fistula	0.2 (1)	0 (0)	0 (0)
	Pneumonia	0.2 (1)	0 (0)	0 (0)
	Pneumonia viral	0.2 (1)	0 (0)	0 (0)
	Small intestinal perforation	0.2 (1)	0 (0)	0 (0)

MedDRA ver.17.1 Incidence % (n)

Among randomized subjects who received study drug in Study 3003, the incidences of infections and serious infections through Week 44 (52 weeks from the initiation of the induction dose) or up to the time of dose adjustment were comparable among the groups and no specific events tended to occur more frequently in the entire study population (Table 39). In the Japanese population, the incidences of infections were 50.0% (2 of 4 subjects) in the placebo group, 62.5% (5 of 8 subjects) in the ustekinumab 90 mg/q12w group, and 88.9% (8 of 9 subjects) in the ustekinumab 90 mg/q8w group, showing a higher incidence in the ustekinumab 90 mg/q8w group, and nasopharyngitis was commonly reported (25.0% [1 of 4 subjects] in the placebo group, 25.0% [2 of 8 subjects] in the ustekinumab 90 mg/q12w group, 44.4% [4 of 9 subjects] in the ustekinumab 90 mg/q8w group). In the Japanese population, serious infections occurred in 2 subjects in the ustekinumab 90 mg/q12w group only (anal abscess; and bacteraemia, 1 subject each). A causal relationship to study drug was ruled out for both events, and the event of anal abscess remained unresolved, and the event of bacteraemia resolved.

Table 39. Serious infections through Week 44 or up to the time of dose adjustment (Study 3003; Randomized subjects who received study drug)

	Maintenance phase (Subcutaneous injections)		
	Placebo (N = 133)	Ustekinumab	
		90 mg/q12w (N = 132)	90 mg/q8w (N = 131)
Infections	49.6 (66)	46.2 (61)	48.1 (63)
Serious injections	2.3 (3)	5.3 (7)	2.3 (3)
Pneumonia	1.5 (2)	0 (0)	0.8 (1)
Ophthalmic herpes zoster	0 (0)	0 (0)	0.8 (1)
Viral infection	0 (0)	0 (0)	0.8 (1)
Anal abscess	0.8 (1)	0.8 (1)	0 (0)
Abdominal infection	0 (0)	0.8 (1)	0 (0)
Appendicitis	0 (0)	0.8 (1)	0 (0)
Bacteraemia	0 (0)	0.8 (1)	0 (0)
Campylobacter gastroenteritis	0 (0)	0.8 (1)	0 (0)
Gastroenteritis	0 (0)	0.8 (1)	0 (0)
Gastroenteritis viral	0 (0)	0.8 (1)	0 (0)
Postoperative wound infection	0 (0)	0.8 (1)	0 (0)

MedDRA ver.17.1 Incidence % (n)

In all randomized and non-randomized subjects who received study drug in Study 3003, the occurrence of infections and serious infections through Week 44 (52 weeks from the initiation of the induction dose) is as follows. The incidences of infections were 50.0% (121 of 242 subjects) in the placebo-treated group and 42.2% (488 of 1157 subjects) in the ustekinumab-treated group, and the incidences of serious infections were 2.1% (5 of 242 subjects) in the placebo-treated group and 3.2% (37 of 1157 subjects) in the ustekinumab-treated group, and no specific events tended to occur more frequently. In the Japanese population, the incidences of infections were 50.0% (4 of 8 subjects) in the placebo-treated group and 67.1% (47 of 70 subjects) in the ustekinumab-treated group, and the incidences of serious infections were 0% (0 of 8 subjects) in the placebo-treated group and 8.6% (6 of 70 subjects) in the ustekinumab-treated group. Serious infections reported by ≥2 subjects in the Japanese population were anal abscess, none of which were classified as adverse drug reactions, and the outcome was reported as "resolved" for 1 case and "unresolved" for the other case.

Among 605 subjects who continued to receive ustekinumab after Week 44 (a mean follow-up period of 68.8 weeks) in Study 3003, the incidences of serious infections[10)] between the Week 44 database lock and October 1, 2015 were 4.5% (27 of 605 subjects) in the entire study population and 4.9% (2 of 41 subjects) in the Japanese population. In the entire study population, serious infections reported by ≥2 subjects were anal abscess (8 subjects), pneumonia (2 subjects), and pyelonephritis (2 subjects). In the Japanese population, serious infections reported were anal abscess (1 subject) and clostridium difficile infection (1 subject). Between October 1, 2015 and August 31, 2016, serious infections were reported by 16 subjects in the entire study population and 1 subject in the Japanese population. Those reported by ≥2 subjects in the entire study population were anal abscess, cellulitis, gastroenteritis, and perirectal abscess (2 subjects each). No serious infections were reported by ≥2 subjects in the Japanese population.

Serious infections including tuberculosis are important potential risks of ustekinumab, which are assessed periodically. According to the latest Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report (the period covered, January 1, 2015 to December 31, 2015) and a periodic safety update report (6th; the period

[10)] Events in the MedDRA SOC Infections and infestations

covered, January 1, 2014 to December 31, 2014), ustekinumab was not associated with an increased risk of serious infections including tuberculosis in Japan or overseas. Tuberculosis occurred in 1 subject in the placebo group in Study 3003. Opportunistic infections occurred in 1 subject in the ustekinumab 6 mg/kg group in Study 3001 (meningitis listeria; serious; outcome, resolved), 1 subject in the placebo group in Study 3002 (oesophageal candidiasis; non-serious), and 1 subject in the ustekinumab-treated group in Study 3003 (oesophageal candidiasis; non-serious).

Infections are listed in the sections of warnings, important precautions, clinically significant adverse reactions, etc., in the current package insert in Japan, and similar warnings and precautions should be provided also for patients with CD. The occurrence of infections will be watched for also after the market launch.

PMDA's view:
In Studies 3001, 3002, and 3003, there were no major differences in the occurrence of infections between placebo- and ustekinumab-treated subjects (Table 38, Table 39), and there was no particularly problematic trend in the occurrence of infections in the Japanese population compared to the entire study population.

Although there were no major problems about infections in Studies 3001, 3002, and 3003, in accordance with warnings and precautions in the package insert for the approved indications of psoriasis vulgaris and psoriatic arthritis, adequate attention should be paid to the possible occurrence of infections also in patients with CD. It is necessary to collect information on the occurrence of infections via post-marketing surveillance etc.

7.R.3.3.2 Infusion reactions following an intravenous dose

The applicant's explanation of the occurrence of infusion reactions etc. following an intravenous dose of ustekinumab:
Adverse events (excluding laboratory abnormalities) occurring during or within 1 hour after intravenous infusion of study drug were analyzed as infusion reactions. In Studies 3001 and 3002, the incidences of infusion reactions were 2.4% (11 of 466 subjects) in the placebo group, 3.6% (17 of 471 subjects) in the ustekinumab 130 mg group, and 2.6% (12 of 470 subjects) in the ustekinumab 6 mg/kg group, and those events reported by ≥2 subjects in any group are shown in Table 40.

Table 40. Infusion reactions reported by ≥2 subjects in any group (Pooled analysis of Studies 3001 and 3002)

	Induction phase (Single intravenous infusion)		
	Placebo (N = 466)	Ustekinumab	
		130 mg (N = 471)	6 mg/kg (N = 470)
All infusion reactions	2.4 (11)	3.6 (17)	2.6 (12)
Nausea	0.2 (1)	0 (0)	0.9 (4)
Dysgeusia	0 (0)	0 (0)	0.4 (2)
Pyrexia	0.2 (1)	0.4 (2)	0.2 (1)
Urticaria	0 (0)	0.4 (2)	0.2 (1)
Flushing	0.4 (2)	0.2 (1)	0.2 (1)
Headache	0.6 (3)	0.6 (3)	0 (0)
Pruritus	0.2 (1)	0.6 (3)	0 (0)
Body temperature increased	0 (0)	0.4 (2)	0 (0)

MedDRA ver.17.1 Incidence % (n)

The incidences of infusion reactions in patients who received intravenous study drug[11)] in Study 3003 were 2.5% (12 of 476) in patients who were not in CR to ustekinumab in Study 3001 or 3002 and received intravenous placebo in Study 3003 and 1.8% (5 of 285) in patients who were not in CR to placebo in Study 3001 or 3002 and received intravenous ustekinumab 130 mg in Study 3003, showing no trend towards a higher incidence in patients who received intravenous ustekinumab.

Among infusion reactions observed in Studies 3001, 3002, and 3003, adverse events of anaphylaxis or anaphylactoid reactions[12)] were analyzed. As a result, 1 subject who received intravenous placebo had dyspnoea, flushing, and throat tightness, 1 subject who received intravenous ustekinumab (ustekinumab 6 mg/kg group) had presyncope, flushing, and dysgeusia, and 1 subject who received intravenous ustekinumab (ustekinumab 130 mg group) had body temperature increased, chest discomfort, flushing, infusion site extravasation, and urticaria. Except for severe dyspnoea reported by 1 subject who received intravenous placebo, all those events were mild or moderate in severity.

None of Japanese patients who received intravenous study drug in Study 3001, 3002, or 3003 had infusion reactions following administration of ustekinumab.

PMDA's view:
In Studies 3001 and 3002, there was no trend towards a higher incidence of infusion reactions following an intravenous dose of ustekinumab compared to placebo (Table 40). No serious anaphylaxis-related adverse events occurred in Study 3001, 3002, or 3003. However, as infusion reactions or anaphylaxis may occur following intravenous administration of ustekinumab, ustekinumab should be used at a facility capable of taking measures promptly in response to infusion reactions, anaphylaxis, etc. and patients should be monitored closely following the start of infusion. It is necessary to collect information on infusion reactions and anaphylaxis-related events via post-marketing surveillance etc.

7.R.3.3.3 Injection site reactions and hypersensitivity following subcutaneous administration

The applicant's explanation of the occurrence of injection site reactions and hypersensitivity following subcutaneous administration of ustekinumab:
The incidence of injection site reactions through Week 44 or up to the time of dose adjustment in randomized subjects who received study drug in Study 3003 is shown in Table 41. The incidences of hypersensitivity (rash or urticaria) were 3.8% (5 of 133 subjects) in the placebo group, 3.0% (4 of 132 subjects) in the ustekinumab 90 mg/q12w group, and 5.3% (7 of 131 subjects) in the ustekinumab 90 mg/q8w group for rash.

[11)] To maintain the blind, both SC and IV administrations were given to patients not in CR in Study 3001 or 3002.
[12)] anaphylactic reaction, pyrexia, chills, rigors, hypotension, hypertension, bronchospasm, laryngospasm, wheezing, dyspnoea, syncope, presyncope, urticaria, angioedema, pruritus generalised, flushing, rash, nausea

Table 41. Incidence of injection site reactions[a)] through Week 44 or up to the time of dose adjustment (Study 3003; Randomized subjects who received study drug)

	Maintenance phase (Subcutaneous injections)		
	Placebo	Ustekinumab	
		90 mg/q12w	90 mg/q8w
N	133	132	131
Injection site erythema	0 (0)	0.8 (1)	5.3 (7)
Injection site bruising	0 (0)	0 (0)	1 (0.8)
Injection site nerve damage	0 (0)	0 (0)	1 (0.8)
Injection site paraesthesia	0 (0)	0 (0)	1 (0.8)
Injection site rash	0 (0)	0 (0)	1 (0.8)
Injection site swelling	0 (0)	0 (0)	1 (0.8)
Injection site pain	0.8 (1)	1.5 (2)	0 (0)
Injection site urticaria	0 (0)	0.8 (1)	0 (0)
Injection site vesicles	0 (0)	0 (0)	0.8 (1)

MedDRA ver.17.1 Incidence % (n)
a) Events identified by PTs containing "injection site"

In all subjects who received subcutaneous study drug in Study 3003, the incidences of injection site reactions through Week 44 were 1.7% (18 of 1032 subjects) in the placebo-treated group and 3.0% (28 of 947 subjects) in the subcutaneous ustekinumab-treated group, and injection site erythema was commonly reported.

No serious or severe events occurred. No administration site reactions were reported in the Japanese population.

PMDA's view:
Although there was no trend towards evidently higher incidences of injection site reactions and hypersensitivity with ustekinumab compared to placebo in Study 3003, it is necessary to collect information on the occurrence of administration site reactions via post-marketing surveillance etc.

7.R.3.3.4 Malignancies

The applicant's explanation of the occurrence of malignancies:
No malignancies were reported in ustekinumab-treated subjects through Week 8 in Study 3001 or 3002. In randomized subjects who received study drug in Study 3003, malignancies reported through Week 44 were basal cell carcinoma (1 subject in the placebo group, 1 subject in the ustekinumab 90 mg/q8w group). Their causal relationship to study drug was ruled out, and these events were not classified as adverse drug reactions. Among non-randomized subjects in Study 3003, basal cell carcinoma; squamous cell carcinoma of skin; and small intestine adenocarcinoma and carcinoid tumour (1 subject each) occurred in the ustekinumab-treated group and squamous cell carcinoma (1 subject) occurred in the placebo-treated group, of which small intestine adenocarcinoma and carcinoid tumour were classified as adverse drug reactions.

In 605 subjects who continued to receive ustekinumab after Week 44 in Study 3003 (a mean follow-up period of 68.8 weeks), malignancies reported between the Week 44 database lock and October 1, 2015 were basal cell carcinoma; chronic myeloid leukaemia; and seminoma (1 subject each), but no specific events tended to occur more frequently. Between October 1, 2015 and August 31, 2016, 1 case of basal cell carcinoma was reported in the entire study population.

In the Japanese population, no malignancies were reported in Study 3001, 3002, or 3003 (including the extension phase after Week 44 [until August 31, 2016]).

In CD clinical studies combined,[13] malignancies occurred in 2 of 943 placebo-treated subjects (0.58 cases/100 subject-years) (pooled data from placebo-treated periods) and 7 of 1749 ustekinumab-treated subjects (0.63 cases/100 subject-years) (pooled data from ustekinumab-treated periods), and there were no major differences between ustekinumab- and placebo-treated subjects. With regard to malignancies in clinical studies in the approved indications for ustekinumab, malignancies occurred in 3 of 733 placebo-treated subjects (1.65 cases/100 subject-years) and 35 of 3117 ustekinumab-treated subjects (1.37 cases/100 subject-years) in psoriasis vulgaris clinical studies[14] and 0 of 379 placebo-treated subjects (0 cases/100 subject-years) and 3 of 1018 ustekinumab-treated subjects (0.35 cases/100 subject-years) in psoriatic arthritis clinical studies.[15] There was no trend towards a higher incidence of malignancies in patients with CD compared to patients with psoriasis vulgaris.

Malignancy is listed in the sections of warnings, careful administration, important precautions, etc. in the current package insert in Japan. Although there is no clear association between ustekinumab and malignancy at present, as ustekinumab has a selective immunosuppressive effect and may increase the risk of malignancy, the occurrence of malignancies will be watched for also after the market launch.

PMDA's view:
Although at present, there is no particular trend towards an increased risk of malignancy associated with ustekinumab in patients with CD, it is necessary to continue to collect information via post-marketing surveillance etc.

7.R.3.3.5 Serious neurological disorder

The applicant's explanation of the occurrence of serious neurological disorder:
No cases of serious neurological disorder such as progressive multifocal leukoencephalopathy, multiple sclerosis, and peripheral demyelination were observed in CD clinical studies. In Study 3003, 1 subject (a non-Japanese patient) had demyelination (non-serious), which was demyelinating disease, meeting the exclusion criteria. Thus, this subject was withdrawn from the study.[16] In clinical studies in the approved indications for ustekinumab, 1 subject in Study C0743T09 (psoriasis vulgaris) had reversible posterior leukoencephalopathy syndrome, but recovered (*Arch Dermatol.* 2011; 147: 1197-1202).

PMDA's view:
Although at present, there is no particular trend towards an increased risk of serious neurological disorder associated with ustekinumab in patients with CD, it is necessary to continue to collect information via post-marketing surveillance etc.

[13] Study C0379T07 (28 weeks), Study C0743T26 (36 weeks), subjects in Study 3001 who did not enter Study 3003 (through Week 20), subjects in Study 3002 who did not enter Study 3003 (through Week 20), and Study 3003 (through Week 44)
[14] Study C0379T04 (52 weeks), Study C0743T08 (52 weeks), Study C0743T09 (52 weeks), and Study C0743T12 (52 weeks)
[15] Study C0743T10 (36 weeks), Study CNTO1275PSA3001 (52 weeks), and Study CNTO1275PSA3002 (60 weeks)
[16] The subject was not in CR to intravenous placebo in Study 3001, and received intravenous ustekinumab 130 mg at Week 0 of Study 3003 and a single subcutaneous injection of ustekinumab 90 mg at Week 8. About 2 months after the start of Study 3003, the subject experienced dizziness, oral numbness, visual symptoms, etc.

7.R.3.4 Anti-ustekinumab antibodies

The applicant's explanation of the incidence of anti-ustekinumab antibody production in CD patients treated with ustekinumab:

Among 1154 patients treated with ustekinumab and assessed for anti-ustekinumab antibodies in Studies 3001, 3002, and 3003, 27 (2.3%) were positive for anti-ustekinumab antibodies, but had no infusion reactions, etc. There were no Japanese patients positive for anti-ustekinumab antibodies in Study 3001 or 3002, and 1 Japanese patient was antibody-positive in Study 3003. There were no patients who were positive for anti-ustekinumab antibodies and experienced adverse events related to study drug.

PMDA's view:

There was no trend towards a higher incidence of anti-ustekinumab antibody production in patients with CD in Studies 3001, 3002, and 3003 compared to that in Japanese clinical studies in the approved indications of psoriasis vulgaris and psoriatic arthritis (6.5% [Stelara Subcutaneous Injection 45 mg Syringe package insert]). At present, there is no particular problem as to anti-ustekinumab antibody production in patients with CD.

7.R.3.5 Post-marketing safety information

The applicant's explanation of post-marketing safety information on ustekinumab:

According to the latest Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report (the period covered, January 1, 2015 to December 31, 2015), the estimated patient exposure to ustekinumab between December 31, 2008 and December 31, 2015 was 551,966 patient-years worldwide. A total of 6692 serious adverse events were reported by December 31, 2015 in marketing experience, and the main adverse events were psoriasis (218 events), myocardial infarction (128 events), pneumonia (108 events), psoriatic arthropathy (94 events), depression (82 events), death (69 events), cerebrovascular accident (67 events), cellulitis (54 events), and prostate cancer (52 events).

A multicenter, prospective, observational study has been conducted overseas to evaluate the long-term safety and track clinical status of patients with psoriasis who are candidates for systemic therapy (Psoriasis Longitudinal Assessment and Registry) (*J Drugs Dermatol.* 2012; 11: 1210-1217). This observational study included patients receiving biologics other than ustekinumab and patients not receiving biologic therapy as well as patients receiving ustekinumab. As of the latest data cutoff date, August 23, 2014, 12,093 patients were registered with a median follow-up period of 3.3 years, and data representing a cumulative exposure of 40,388 patient-years were obtained. As a result, no major differences between the ustekinumab-treated group and other groups were observed for the occurrence of adverse events, serious adverse events, death from any cause, serious cardiovascular events, malignancies, and serious infections.

Based on the above, post-marketing safety information on ustekinumab has raised no new safety issues at present.

PMDA confirmed that post-marketing safety information on ustekinumab for the approved indications has raised no new safety issues at present.

7.R.4 Clinical positioning

The applicant's explanation of the clinical positioning of ustekinumab:

In Japan, treatment of CD is based on the treatment guidelines (2014 revised version of the Diagnostic Criteria/Treatment Guidelines for ulcerative colitis and Crohn's disease, March 31, 2015, Health and Labour Sciences Research Grant, Rare/Intractable Disease Project, "Research on intractable inflammatory bowel disease" [Leader, Suzuki], *2014 Research Report, Supplement*. 2015;19-22) etc. and as drug therapies for inducing remission, 5-aminosalicylic acid (5-ASA) preparations, corticosteroids, antibiotics, azathioprine (AZA), 6-mercaptopurine (6-MP), and TNF antagonists are used according to the severity of the disease. As drug therapies for maintaining remission, in addition to 5-ASA preparations, AZA, and 6-MP, TNF antagonists are used in patients induced into remission with TNF antagonists. Currently in Japan, biologic agents that can be used in patients who have had an inadequate response or are intolerant to conventional systemic therapy (5-ASA, corticosteroids, immunomodulators, etc.) are TNF antagonists only. However, among patients who receive TNF antagonist therapies for CD, 20% to 40% are primary non-responders and even among those with an initial response, about 40% lose their response over time. Thus, a new treatment option is needed. As ustekinumab is a selective IL-12/23 inhibitor and has a different mechanism of action from anti-TNF agents, it can become a new treatment option.

PMDA's view:

Taking also account of patients included in Studies 3001 and 3002 (Table 5 and Table 12), ustekinumab should be indicated for patients who have had an inadequate response to existing biologic agents, anti-TNF agents, or conventional therapy (5-ASA, corticosteroids, immunomodulators, etc.). While Study 3001 confirmed the efficacy and safety of ustekinumab in patients who had failed anti-TNF therapy, the efficacy of ustekinumab in primary non-responders to anti-TNF therapy is undetermined at present [see Section 7.R.2.1.2], and no head-to-head efficacy and safety studies of ustekinumab vs. anti-TNF therapy have been performed. Given these points etc., there is no evidence for actively recommending ustekinumab as the first-line biologic. However, as ustekinumab has a different mechanism of action from anti-TNF agents, it can become a new biologic option. Since the efficacy and safety of ustekinumab in combination with other biologics, anti-TNF agents, in patients with CD, have not been confirmed, ustekinumab should not be used concomitantly with other biologics at present.

7.R.5. Indications

Studies 3001, 3002, and 3003 demonstrated the efficacy of ustekinumab induction and maintenance therapy [see Section 7.R.2], and its safety was considered acceptable as long as appropriate precautions are provided [see Section 7.R.3]. Thus, PMDA considers that there is no problem with the intended population of patients with moderately to severely active CD who have had an inadequate response to conventional therapy. However, as ustekinumab is available as an intravenous formulation for induction dosing and a subcutaneous formulation for maintenance dosing, separate indications for the intravenous and subcutaneous formulations should be established appropriately, taking account of the study population, the results of the primary endpoint, etc. in Studies 3001, 3002, and 3003.

The indications for ustekinumab will be finalized, taking account of comments from the Expert Discussion.

7.R.6 Dosage and administration

7.R.6.1 Initial induction regimen

The applicant proposed the following induction regimen of ustekinumab for patients with active CD:

> "The usual adult initial dosage of Ustekinumab (Genetical Recombination), infused intravenously as a single dose: body weight/dose, ≤55 kg/260 mg; >55 kg and ≤85 kg/390 mg; >85 kg/520 mg"

The applicant's rationale for this regimen:

The dosing regimen of ustekinumab selected for Studies 3001 and 3002 was based on the results of foreign phase II studies in patients with moderately to severely active CD (Study C0379T07 [CTD5.3.5.1.4] and Study C0743T26 [CTD5.3.5.1.5]; Reference data). Study C0379T07 compared intravenous ustekinumab 4.5 mg/kg with subcutaneous ustekinumab 90 mg, which showed higher efficacy (CR rate, etc.) and a trend towards a rapid decrease in inflammation-related markers following intravenous administration. Thus, intravenous administration was chosen for Study C0743T26. Intravenous doses of 1 mg/kg, 3 mg/kg, and 6 mg/kg of ustekinumab were selected for Study C0743T26. The primary endpoint for Study C0743T26, i.e. the CR rates at Week 6 were 23.5% (31 of 132 subjects) in the placebo group, 36.6% (48 of 131 subjects) in the ustekinumab 1 mg/kg group, 34.1% (45 of 132 subjects) in the ustekinumab 3 mg/kg group, and 39.7% (52 of 131 subjects) in the ustekinumab 6 mg/kg group, and the results of the clinical remission rate and other efficacy endpoints as well as the primary endpoint showed that the 6 mg/kg dose was the most effective dose. Regarding safety, there was no trend towards a dose-dependent increase in adverse events in Study C0743T26. Based on the above, the 6 mg/kg dose was selected for Studies 3001 and 3002. To simplify dosing, weight-range based ustekinumab doses approximating 6 mg/kg (≤55 kg [260 mg], >55 kg and ≤85 kg [390 mg], >85 kg [520 mg]) were selected for Studies 3001 and 3002. A 130 mg fixed dose was chosen as a dose lower than 6 mg/kg and intermediate to the 1 and 3 mg/kg doses.

Though the primary endpoint of the CR rate at Week 6 was similar between the 130 mg and 6 mg/kg groups in Studies 3001 and 3002, the clinical remission rate at Week 8 was higher in the 6 mg/kg group than in the 130 mg group in both Studies 3001 and 3002 [see Section 7.R.2.1], and there were no major differences in safety between the 6 mg/kg and 130 mg groups [see Sections 7.1 and 7.2]. Thus, an initial induction regimen of a one-time intravenous infusion of ustekinumab 6 mg/kg (≤55 kg [260 mg], >55 kg and ≤85 kg [390 mg], >85 kg [520 mg]) was considered justified.

PMDA's view on the initial induction regimen of ustekinumab:

Studies 3001 and 3002 confirmed the efficacy of ustekinumab 130 mg and 6 mg/kg and showed a trend towards a higher clinical remission rate at Week 8 in the 6 mg/kg group than in the 130 mg group [see Section 7.R.2], and there were no relevant differences in safety between the 130 mg and 6 mg/kg groups [see Section 7.R.3]. Thus, the proposed initial induction dose of 6 mg/kg and weight-range based ustekinumab doses approximating 6 mg/kg (≤55 kg [260 mg], >55 kg and ≤85 kg [390 mg], >85 kg [520 mg]) for patients with CD are acceptable.

The initial induction regimen of ustekinumab will be finalized, taking account of comments from the Expert Discussion.

7.R.6.2 Maintenance regimen

The applicant's explanation of the rationale for the proposed maintenance regimen of ustekinumab: "The usual adult maintenance dosage is a subcutaneous 90 mg dose of Ustekinumab (Genetical Recombination) administered 8 weeks after the initial intravenous infusion induction dose, then every 8 weeks thereafter. Dosing every 12 weeks after the first subcutaneous dose may be acceptable for patients with a lower inflammatory burden. Patients who inadequately respond to 90 mg subcutaneous dosing every 12 weeks may be dosed every 8 weeks."

In a foreign phase II study (Study C0743T26 [CTD5.3.5.1.5] Reference data), responders to intravenous ustekinumab were re-randomized and received subcutaneous ustekinumab 90 mg or placebo at Weeks 8 and 16. As a result, ustekinumab showed a benefit in terms of clinical remission at Week 22. Thus, a maintenance regimen of ustekinumab 90 mg SC q8w was selected for Study 3003. A 90 mg SC q12w regimen was included in the study to explore a lower dosing regimen since it is the approved dosing regimen for psoriasis.

Although the results of Study 3003 showed higher efficacy in both the ustekinumab 90 mg/q12w and 90 mg/q8w groups compared to the placebo group, a usual maintenance dosage of ustekinumab 90 mg administered subcutaneously every 8 weeks (90 mg/q8w) was proposed for the following reasons.

● For both 90 mg/q12w and 90 mg/q8w, a significant difference from placebo was seen for the primary endpoint of the clinical remission rate at Week 44, but the rates were 35.9% (47 of 131 subjects) in the placebo group, 48.8% (63 of 129 subjects) in the 90 mg/q12w group, and 53.1% (68 of 128 subjects) in the 90 mg/q8w group, showing a trend towards a higher rate in the 90 mg/q8w group.

● The clinical remission rates at Week 44 among anti-TNF naïve patients who entered from Study 3002 were 49.0% (25 of 51 subjects) in the placebo group, 56.6% (30 of 53 subjects) in the 90 mg/q12w group, and 65.4% (34 of 52 subjects) in the 90 mg/q8w group, showing a trend towards a higher rate in the 90 mg/q8w group.

● The clinical remission rates at Week 44 among patients who were in clinical remission at baseline of Study 3003 were 45.6% (36 of 79 subjects) in the placebo group, 56.4% (44 of 78 subjects) in the 90 mg/q12w group, and 66.7% (52 of 78 subjects) in the 90 mg/q8w group, showing a trend towards a higher rate in the 90 mg/q8w group.

The clinical remission rates at Week 44 by serum CRP concentration at baseline of Study 3001 or 3002 were 43.9% (25 of 57 subjects) in the 90 mg/q12w group and 53.3% (32 of 60 subjects) in the 90 mg/q8w group in the subgroup of CRP >1.0 mg/dL, showing a higher rate with 90 mg/q8w. Meanwhile, the clinical remission rates in the subgroup of CRP ≤0.5 mg/dL were 50.0% (22 of 44 subjects) in the 90 mg/q12w group and 53.5% (23 of 43 subjects) in the 90 mg/q8w group, showing no major differences between the groups. Hence, a maintenance dosage of a subcutaneous 90 mg dose of ustekinumab administered 8 weeks after the initial intravenous infusion induction dose, then every 12 weeks thereafter, was proposed for patients with a lower inflammatory burden.

PMDA's view on the maintenance regimen of ustekinumab:

The primary endpoint of the clinical remission rate at Week 44 in Study 3003 tended to be slightly higher in the 90 mg/q8w group compared to the 90 mg/q12w group (53.1% and 48.8%, respectively[17]), but no clear differences were seen. Although the applicant used the results of subgroup analyses as the basis for the proposed maintenance regimen of ustekinumab 90 mg dosing every 8 weeks, there are limitations to justifying the proposed dosing regimen based on the results of some subgroup analyses.

In Study 3003, the proportions of patients who met the loss of response criteria (Table 4) through Week 32 were 21.9% (28 of 128 subjects) in the 90 mg/q8w group and 22.5% (29 of 129 subjects) in the 90 mg/q12w group, showing no major differences between the groups. Furthermore, based on an analysis including data after dose adjustment in patients who met the loss of response criteria in Study 3003,[18] the clinical remission rates at Week 44 were 58.1% (75 of 129 subjects) in the 90 mg/q12w group and 60.2% (77 of 128 subjects) in the 90 mg/q8w group, showing no major differences between the groups. When patients who lost response to 90 mg dosing every 12 weeks switched to q8w dosing frequency, patients initiating q12w dosing achieved clinical remission at a proportion that was similar to patients initiating q8w dosing.

According to the EU labeling, the maintenance dosage of ustekinumab is 90 mg administered subcutaneously every 12 weeks, and patients who have lost response to dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks.

Based on the above, there is no particular problem with a usual maintenance dosage of 90 mg administered subcutaneously every 12 weeks, and the dosing interval may be shortened to every 8 weeks in patients who have lost response [see Section 7.R.6.3]. A final conclusion will be made, taking account of comments from the Expert Discussion.

7.R.6.3 Shortening of dosing interval upon loss of response

The applicant's explanation of the justification for shortening the dosing interval to every 8 weeks in patients who have lost response to ustekinumab 90 mg dosing every 12 weeks:

In Study 3003, patients in the ustekinumab 90 mg/q12w group who lost response were to switch to q8w dosing frequency [see Section 7.3]. In the primary population of Study 3003, 22.5% (29 of 129) of subjects in the 90 mg/q12w group met the loss of response criteria and switched to q8w dosing frequency. Of the 29 subjects, 55.2% (16 of 29 subjects) regained CR and 41.4% (12 of 29 subjects) were in clinical remission 16 weeks after switching to the 8-weekly dose. In the 29 subjects, the change in the CDAI score at 16 weeks after switching to the 8-weekly dose (mean ± SD) was −124.5 ± 98.4. The above results indicated that patients who were in CR to ustekinumab and subsequently lost response showed a certain level of improvement after shortening the dosing interval from every 12 weeks to every 8 weeks. Regarding the safety of ustekinumab with a reduced dosing interval, as there were no relevant differences in the occurrence of adverse events between the 90 mg/q12w and 90 mg/q8w groups [see Section 7.R.3], no problems should arise also with dosing every 8 weeks as long as similar measures are taken as with dosing every 12 weeks.

[17] Based on the analysis using a corrected CDAI score, the clinical remission rates were 53.5% and 48.8%, respectively (Table 34).

[18] In the primary analysis, all patients who met the loss of response criteria were handled as "patients not in clinical remission." In this analysis, the following data (a) and (b) from patients who met the loss of response criteria were also assessed: (a) Data after dose adjustment in patients in the 90 mg/q12w group who met the loss of response criteria and had a dose adjustment to 90 mg q8w, (b) Data after loss of response in patients in the 90 mg/q8w group who met the loss of response criteria

PMDA considers that patients who have lost response to ustekinumab 90 mg/q12w may switch to q8w dosing frequency, but will make a final conclusion, taking account of comments from the Expert Discussion.

7.R.6.4 Timing of assessment for continued therapy

The applicant's explanation of the timing of assessment for discontinuation of treatment with ustekinumab in patients who do not respond or have lost response to ustekinumab:

Four hundred sixty-seven patients not in CR at 8 weeks after the initial intravenous dose of ustekinumab in Study 3001 or 3002 received subcutaneous ustekinumab 90 mg at Week 0 of Study 3003, and 50.5% (236 of 467) of these patients achieved CR at Week 8. Of those patients who continued to receive subcutaneous ustekinumab 90 mg every 8 weeks, 50.2% (126 of 251 patients) were in clinical remission at Week 44. Patients in the 90 mg/q12w group who met the loss of response criteria (Table 4) during Study 3003 switched from q12w maintenance therapy to q8w maintenance therapy. Patients who did not show improvement in disease activity 16 weeks after dose adjustment, as assessed by the investigator, were to be discontinued from study drug administration.

Based on the above, patients should be assessed for the efficacy of ustekinumab to determine whether to continue treatment by the second subcutaneous dose or 16 weeks after shortening the dosing interval.

Based on the results of Study 3003 and the applicant's explanation, PMDA considers that patients should be assessed for the therapeutic effects of ustekinumab to determine whether to continue treatment by the second subcutaneous dose or 16 weeks after shortening the dosing interval, but will make a final conclusion, taking account of comments from the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant is planning post-marketing surveillance as shown in Table 42.

Table 42. Outline of specified use-results survey (draft)

Objective	**To evaluate the long-term safety and efficacy of ustekinumab in routine clinical settings.**
Survey method	**Central registration system**
Planned survey period	**4 years (enrollment period, 2 years)**
Planned sample size	**300 patients**
Planned number of sites	**Approximately 100 sites**
Population	**Patients with moderately to severely active CD who have had an inadequate response to conventional therapy**
Observation period	**52 weeks**
Main survey items	**· Patient characteristics (complications, past medical history, etc.)** **· Prior therapies for CD, concomitant medications, concomitant therapies** **· Dose of ustekinumab, drug interruption and its reason** **· CDAI, endoscopy, global improvement** **· Occurrence of adverse events** **· Information to be collected with special care: serious hypersensitivity, serious infections, malignancy, etc.**

PMDA considers that the specified use-results survey (draft) presented by the applicant should also cover the following issues, but will make a final conclusion, taking account of comments from the Expert Discussion.

● Dosing interval of ustekinumab and efficacy with an altered dosing interval
● Doses of concomitant corticosteroids (withdrawal of corticosteroids)
● Development of malignancy during long-term treatment with ustekinumab

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that ustekinumab has efficacy in the treatment of patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy, and that ustekinumab has acceptable safety in view of its benefits. Ustekinumab is clinically meaningful because it offers a new treatment option for patients with Crohn's disease. PMDA considers that the efficacy, safety, indications, dosage and administration, and post-marketing investigations of ustekinumab need further discussion.

PMDA has concluded that ustekinumab may be approved if ustekinumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

January 27, 2017

Products Submitted for Approval

Brand Name	Stelara Intravenous Infusion 130 mg Stelara Subcutaneous Injection 45 mg Syringe
Non-proprietary Name	Ustekinumab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	March 30, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the products submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, safety, indications, dosage and administration, etc.

At the Expert Discussion, the expert advisors supported PMDA's conclusions on Sections "7.R.2 Efficacy," "7.R.3 Safety," "7.R.5 Indications," and "7.R.6 Dosage and administration" presented in the Review Report (1). The expert advisors commented that it is useful to provide information on efficacy by prior therapy (Review Report (1) Table 31 and Table 32) to healthcare professionals in clinical practice, using information materials for healthcare professionals, etc.

Based on the Review Report (1) and comments from the Expert Discussion, PMDA considered that the indications, precautions for indications, dosage and administration, and precautions for dosage and administration for Stelara Intravenous Infusion 130 mg and Stelara Subcutaneous Injection 45 mg Syringe should be as follows.

1. Stelara Intravenous Infusion 130 mg:

Indication

Induction therapy for moderately to severely active Crohn’s disease (only in patients who have had an inadequate response to conventional therapy)

Precautions for Indication

- Use Stelara in patients who still have evident clinical symptoms related to Crohn’s disease despite appropriate prior treatment, such as nutritional therapy and other medications (5-aminosalicylic acid preparations, corticosteroids, azathioprine, etc.).

Dosage and administration

The usual adult initial dosage of Ustekinumab (Genetical Recombination), infused intravenously as a single dose (induction therapy):

Body weight	Dose
≤55 kg	260 mg
>55 kg and ≤85 kg	390 mg
>85 kg	520 mg

Precautions for Dosage and Administration

- The initial induction dose is followed 8 weeks later by subcutaneous maintenance dosing of Ustekinumab (Genetical Recombination). For the maintenance dosage regimen, see the package insert for Stelara Subcutaneous Injection 45 mg Syringe.

2. Stelara Subcutaneous Injection 45 mg Syringe:

Indication

Maintenance therapy for moderately to severely active Crohn's disease (only in patients who have had an inadequate response to conventional therapy)

Precautions for Indication

- Use Stelara in patients who still have evident clinical symptoms related to Crohn's disease despite appropriate prior treatment, such as nutritional therapy and other medications (5-aminosalicylic acid preparations, corticosteroids, azathioprine, etc.).

Dosage and administration

The usual adult maintenance dosage is a subcutaneous 90 mg dose of Ustekinumab (Genetical Recombination) administered 8 weeks after the intravenous infusion induction dose, then every 12 weeks thereafter. The dosing interval may be shortened to every 8 weeks in patients who have lost response.

Precautions for Dosage and Administration

1. The first subcutaneous dose should be given 8 weeks after the initial intravenous infusion induction dose [For the induction dosage regimen, see the package insert for Stelara Intravenous Infusion 130 mg].
2. The dosing interval may be shortened to every 8 weeks at ≥8 weeks after the first subcutaneous dose in patients who have lost response to subcutaneous dosing. Discuss whether to continue treatment if patients show no evidence of therapeutic benefit within 16 weeks after dosing interval reduction, because they may not respond to prolonged treatment.
3. Discuss whether to continue treatment if patients show no response by the second subcutaneous dose, because they may not respond to prolonged treatment.

(Only the statements relevant to the current application are presented.)

1.2 Development of ustekinumab 90 mg pre-filled syringe for subcutaneous injection

The usual maintenance dose of ustekinumab is 90 mg for patients with Crohn's disease, but only the 45 mg formulation (ustekinumab 45 mg pre-filled syringe for subcutaneous injection) is commercially available in Japan. This means that patients requiring a 90 mg dose have to receive 2 subcutaneous injections of the 45 mg formulation. Since the current application does not propose ustekinumab 90 mg pre-filled syringe for subcutaneous injection, PMDA asked the applicant to explain the plan to develop ustekinumab 90 mg pre-filled syringe for subcutaneous injection in Japan.

The applicant's explanation:

If ustekinumab 90 mg pre-filled syringe for subcutaneous injection is introduced, there will be 3 types of drug products: the vial drug product for intravenous infusion for induction therapy, and 45 mg and 90 mg pre-filled syringe drug products for subcutaneous injection for maintenance therapy. Prior to filing the current application, the applicant conducted a survey that asked physicians and pharmacists[19)] in Japan about the need for ustekinumab 90 mg pre-filled syringe for subcutaneous injection. Only a minority of them answered that they would use ustekinumab 90 mg pre-filled syringe for subcutaneous injection, besides the vial drug product (for intravenous infusion for induction therapy) and ustekinumab 45 mg pre-filled syringe (for subcutaneous injection). The majority were not supportive of 90 mg pre-filled syringe, because each medical institution had limits on the number of drugs accepted, and because they were concerned about drug inventory management. The applicant thus saw no strong medical need for ustekinumab 90 mg pre-filled syringe for subcutaneous injection, and therefore excluded the 90 mg pre-filled syringe from the current application. Taking account of requests from patients, healthcare professionals, etc., the applicant will continue to discuss whether to introduce the additional dosage form of ustekinumab 90 mg pre-filled syringe for subcutaneous injection.

PMDA considers that the applicant should continue to consider introducing an additional dosage form of ustekinumab 90 mg pre-filled syringe for subcutaneous injection, taking account of the medical need.

1.3 Risk management plan (draft)

The expert advisors supported PMDA's conclusion presented in Section “7.R.7 Post-marketing investigations” in the Review Report (1).

In view of the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for ustekinumab should include the safety and efficacy specifications presented in Table 43, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 44 and a specified use-results survey presented in Table 45.

[19)] Physicians with experience in the diagnosis and treatment of inflammatory bowel disease and hospital pharmacists, etc.

Table 43. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
· Serious hypersensitivity reactions · Serious infections · Tuberculosis · Interstitial pneumonia	· Malignancy · Cardiovascular events · Exacerbation and new onset of pustular psoriasis/erythrodermic psoriasis · Immunogenicity	· None
Efficacy specification		
· Efficacy of ustekinumab in the treatment of psoriasis vulgaris/psoriatic arthritis in routine clinical settings. · Efficacy of ustekinumab in the treatment of moderately to severely active Crohn's disease in routine clinical settings.		

Table 44. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
· Early post-marketing phase vigilance (Crohn's disease) · Specified use-results survey (psoriasis vulgaris/psoriatic arthritis) · Specified use-results survey (Crohn's disease)	· Early post-marketing phase vigilance (Crohn's disease) · Develop and distribute information materials for healthcare professionals. · Develop and distribute information materials for patients. · Ensure that information on the proper use is provided before the delivery of the product

Table 45. Outline of specified use-results survey (draft)

Objective	To evaluate the long-term safety and efficacy of ustekinumab in routine clinical settings.
Survey method	Central registration system
Planned survey period	4-5 years (enrollment period, 2 years)
Planned sample size	300 patients
Planned number of sites	Approximately 100 sites
Population	Patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy
Observation period	52 weeks (Patients will be followed up for the development of malignancy for 3 years.)
Main survey items	· Patient characteristics (complications, past medical history, etc.) · Prior therapies for Crohn's disease, concomitant medications, concomitant therapies · Dose of ustekinumab, drug interruption and its reason · CDAI, endoscopy, global improvement · Occurrence of adverse events · Key survey items: serious hypersensitivity reactions, serious infections, tuberculosis, malignancy, interstitial pneumonia, demyelinating disease

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.[20)] The inspection revealed the following problem:

Investigators were required to check the efficacy data entered in the Interactive Voice Response System/Interactive Web Response System and then sign the electronic case report forms at study sites. The sponsor did not keep a record of the fact that this procedure had been explained to investigators.

As this problem did not affect the integrity of the studies or assessment of the results, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

[20)] False data at 1 study site overseas for CTD 5.3.5.1.2 were reported [see Section 7.2]. PMDA confirmed that a similar situation did not occur in other studies supporting the current application, etc.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1, CTD 5.3.5.1.2, CTD 5.3.5.1.3-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection showed that the clinical studies as a whole were conducted in compliance with GCP. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following problems associated with a study site and the sponsor, although they did not affect the overall assessment of the studies. PMDA notified the head of the study site and the applicant (the sponsor) of the problems.

Problems found

Study site

- Protocol deviations (non-compliance with the rules for tuberculosis screening)
- Inconsistencies between source documents and CRF, etc. (Crohn's Disease Activity Index items of the number of soft stools, general well-being, and height)

Sponsor

- The sponsor did not appropriately inform investigators and the heads of study sites about some of serious, unexpected adverse drug reactions etc.
- The sponsor did not take necessary actions after they had found the inconsistencies between source documents and CRF, etc. through study site monitoring.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved after modifying the proposed indications and dosage and administration as shown below, with the following condition. Since Stelara Intravenous Infusion 130 mg is a drug with a new route of administration, the re-examination period is 6 years. Since Stelara Subcutaneous Injection 45 mg Syringe is to be used following administration of Stelara Intravenous Infusion 130 mg, the re-examination period for Stelara Subcutaneous Injection 45 mg Syringe is also 6 years. Stelara Intravenous Infusion 130 mg is classified as a biological product, and the drug product is classified as a powerful drug.

Indications

1. Stelara Intravenous Infusion 130 mg:

Induction therapy for moderately to severely active Crohn's disease (only in patients who have had an inadequate response to conventional therapy)

2. Stelara Subcutaneous Injection 45 mg Syringe:

Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:

Psoriasis vulgaris and psoriatic arthritis

Maintenance therapy for moderately to severely active Crohn's disease (only in patients who have had an inadequate response to conventional therapy)

(Underline denotes additions.)

Dosage and Administration

1. Stelara Intravenous Infusion 130 mg:

The usual adult initial dosage of Ustekinumab (Genetical Recombination), infused intravenously as a single dose (induction therapy):

Body weight	Dose
≤55 kg	260 mg
>55 kg and ≤85 kg	390 mg
>85 kg	520 mg

2. Stelara Subcutaneous Injection 45 mg Syringe:

Psoriasis vulgaris and psoriatic arthritis

The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter. If the effect is insufficient, a dose of 90 mg may be used.

Crohn's disease

The usual adult maintenance dosage is a subcutaneous 90 mg dose of Ustekinumab (Genetical Recombination) administered 8 weeks after the intravenous infusion induction dose, then every 12 weeks thereafter. The dosing interval may be shortened to every 8 weeks in patients who have lost response.

(Underline denotes additions.)

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.