**Report on the Deliberation Results**

December 6, 2010

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| [Brand name] | Stelara Subcutaneous Injection 45 mg Syringe |
| [Non-proprietary name] | Ustekinumab (Genetical Recombination) (JAN*) |
| [Applicant] | Janssen Pharmaceutical K.K. |
| [Date of application] | January 21, 2010 |

[Results of deliberation]
In the meeting held on November 29, 2010, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs.

The conditions for approval should be modified as follows.

**After modification**
[Conditions for approval]
The applicant is required to:
1. Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.
2. Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the efficacy and long-term safety of the product, including the occurrence of infections, etc.

**Before modification**
[Conditions for approval]
The applicant is required to:
1. Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.
2. Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the efficacy and long-term safety of the product and the occurrence of infections etc.

(The underlined parts are the changes.)

**Japanese Accepted Name (modified INN)*

**Review Report**

November 10, 2010
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010
[Dosage form/Strength] A solution for injection in a prefilled syringe. Each prefilled syringe (0.5 mL) contains 45 mg of Ustekinumab (Genetical Recombination).
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure] See Figure 1 and Figure 2 below.
Molecular formula: H-chain $C_{2207}H_{3410}N_{582}O_{671}S_{17}$
L-chain $C_{1034}H_{1596}N_{274}O_{337}S_{6}$
Molecular weight: 148,079 to 149,690
Chemical name:

Ustekinumab is a recombinant human IgG1 monoclonal antibody against the p40 subunit of human interleukin-12 and interleukin-23.
Ustekinumab is produced in mouse myeloma (Sp2/0) cells.
Ustekinumab is a glycoprotein (molecular weight, 148,079-149,690) composed of 2 H-chain (γ1-chain) molecules consisting of 449 amino acid residues each and 2 L-chain (κ-chain) molecules consisting of 214 amino acid residues each.

[Items warranting special mention] None
[Reviewing office] Office of New Drug IV

## Heavy Chain

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY   60
                          22-96
SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR PGQGYFDFWG QGTLVTVSSS  120

STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG  180
                    146-202
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP  240
                                  222       228   231
                                  LC        HC    HC      N-Glycan
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS  300
                       263-323
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL  360

TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ  420
  369-427
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK                                    449
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## Light Chain

```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS   60
                       23-88
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ GTKLEIKRTV AAPSVFIFPP  120

SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
                 134-194
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214
                                     HC
```

Figure 1. Heavy and light chains of ustekinumab

Amino acid sequences of the heavy and light chains of ustekinumab are indicated in the single-letter code.
Complementarity-determining regions are underlined.
H-chain K449: partial processing

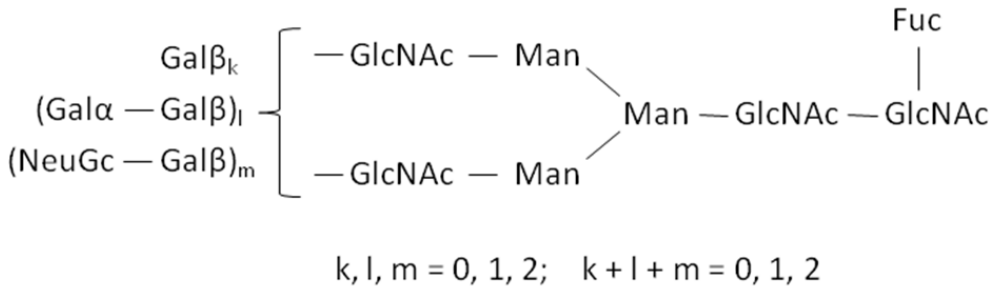



Figure 2. Carbohydrate structure

**Review Results**

November 10, 2010

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010

[Results of review]
Based on the submitted data, the efficacy of the product in the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy has been demonstrated and its safety is acceptable in view of its observed benefits.

Serious adverse drug reactions such as infections may occur following administration of the product. Therefore, prior to the use of the product, the patient's symptoms etc. should be monitored closely and the risks and benefits of the product should be weighed carefully. The risks of the product should be fully explained to the patient as well. It is necessary to closely monitor the course of the disease also after the initiation of treatment. After the market launch, a post-marketing surveillance study focusing on the occurrence of serious infections etc., covering all the patients treated with the product, and a long-term survey to follow the patients for the development of infections and malignancy etc. need to be conducted.

As a result of its review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

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

[Dosage and administration]
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.

[Conditions for approval]
The applicant is required to:
(1) Conduct a post-marketing drug use-results survey, which covers all the patients treated with the

product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.

(2) Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the long-term safety of the product and the occurrence of infections etc.

**Review Report (1)**

October 12, 2010

## I. Product Submitted for Registration

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010
[Dosage form/Strength] A solution for injection in a prefilled syringe. Each prefilled syringe (0.5 mL) contains 45 mg of Ustekinumab (Genetical Recombination).
[Proposed indication]
Moderate to severe psoriasis vulgaris
Psoriatic arthritis with moderate to severe plaque psoriasis
[Proposed dosage and administration]
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.
A dose of 90 mg may be administered in patients weighing >100 kg.

## II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

### 1. Origin or history of discovery and usage conditions in foreign countries etc.

The active substance Ustekinumab (Genetical Recombination) (ustekinumab) is a human immunoglobulin G (IgG) 1κ monoclonal antibody (mAb) against human interleukin (IL)-12/23 p40, developed by Centocor Inc. (the US) (currently Centocor Ortho Biotech Inc.).

Psoriasis vulgaris is an immune-mediated inflammatory keratosis with alternating periods of remissions and flare-ups, characterized by the formation of infiltrative erythematous plaques or irregularly shaped erythematous plaques. Psoriatic arthritis is a rheumatoid factor-negative inflammatory arthritis associated with psoriasis of skin. In general, for patients with mild (body surface area [BSA] involvement of ≤10%) to moderate (BSA involvement of 10%-30%) disease, topical corticosteroids, topical vitamin $D_3$ derivatives, and combination therapy of these agents are used. For patients with moderate to severe disease, phototherapy and systemic therapies (e.g., cyclosporine, and etretinate) are used. Anti-TNF-α agents, infliximab and adalimumab, were approved in January 2010 to treat patients who have had an inadequate response to these conventional therapies.

T cells are believed to be fundamental to the development of the disease and to play a central role in the pathology of the disease. Ustekinumab has a novel mechanism of action of inhibiting the function of T cells by binding with high affinity to IL-12/23 p40, the shared subunit of human IL-12 and IL-23 that are involved in T cell differentiation. Thus, ustekinumab was developed as a therapeutic drug for psoriasis.

The clinical development of ustekinumab for the treatment of psoriasis began in 20[redacted] overseas and ustekinumab was first approved in Canada in December 2008 for the indication of "moderate to severe plaque psoriasis." As of September 2010, ustekinumab has been approved in 52 countries for indications related to psoriasis.

In Japan, the clinical development of ustekinumab for the treatment of psoriasis began in [redacted] 20[redacted]. Based on the claim that Japanese clinical studies etc. have confirmed the efficacy and safety of ustekinumab, the applicant has filed a marketing application for ustekinumab.

**2. Data relating to quality**

***2.A Summary of the submitted data***

Ustekinumab is produced in murine myeloma (Sp2/0) cells, and it is a glycoprotein (molecular weight, 148,079-149,690) composed of two heavy chain (γ1chain, $C_{2207}H_{3410}N_{582}O_{671}S_{17}$; molecular weight, 49,377.29) molecules consisting of 449 amino acid residues each and two light chain (κ-chain, $C_{1034}H_{1596}N_{274}O_{337}S_6$; molecular weight, 23,449.76) molecules consisting of 214 amino acid residues each. Ustekinumab contains a single *N*-linked glycosylation site (Asn299) in the constant region of each heavy chain. The molecule contains a total of 16 disulfide bonds.

**2.A.(1) Drug substance manufacturing process**

**2.A.(1).1) Assembly of the gene expression construct and cell banking**

[redacted].

A genomic library of the cell line A was prepared to clone human anti-IL-12 IgG1 heavy and light chain genes. [redacted]. A master cell bank (MCB) was prepared from the cell line D and a working cell bank (WCB) was

prepared from the MCB. Although bovine serum was used in the process before the selection of the cell line D, no raw materials of animal origin were used thereafter.

**2.A.(1).2) Characterization and control of cell banks**

MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) were characterized as shown in Table 1.

Table 1. Results of characterization of cell banks etc.

| Test | Test results | | | |
|---|---|---|---|---|
| | MCB | WCB | | CAL |
| | Lot: a | Lot: b | Lot: c | Lot: d |
| Isoenzyme analysis | Of mouse origin | Of mouse origin | Of mouse origin | Of mouse origin |
| Double immunodiffusion | NT | [redacted] | | NT |
| cDNA sequence | cDNA sequence/deduced amino acid sequence agreed with the reference sequence. | NT | NT | Consistent with MCB |
| Analysis of patterns of DNA inserts | Consistent with the banding patterns of the heavy and light chain vectors | NT | NT | Consistent with MCB |
| Gene copy number | [redacted] | NT | NT | [redacted] |
| [redacted] | NT | NT | NT | [redacted] |

NT: Not tested

Purity tests as shown in Table 2 were performed and no viral or non-viral infectious agents were detected other than ecotropic recombinant virus (ERV) and A-type and C-type retrovirus-like particles in the MCB, WCB, and CAL, within the scope of the tests performed.

Table 2. Results of tests for purity of cell banks etc.

| Test | | | Acceptance criteria | Test results | | | |
|---|---|---|---|---|---|---|---|
| | | | | MCB | WCB | | CAL |
| | | | | Lot: a | Lot: b | Lot: c | Lot: d |
| Sterility | | | Negative | Negative | Negative | Negative | NT |
| Mycoplasma testing (culture method and non-cultural method) | | | Negative | Negative | Negative | Negative | NT |
| Tests for retroviruses and other endogenous viruses | Infectivity assays | Assay for ERV[a)] | Report results only | Negative | Negative | Negative | NT |
| | | $S^+L^-$ focus assay[b)] | Report results only | Negative | Negative | Negative | NT |
| | | XC plaque assay[c)] | Report results only | Negative | Negative | Negative | NT |
| | | Co-cultivation assay for ERV[a)] | Report results only | ERV detected | ERV detected | ERV detected | ERV detected |
| | | Mink cell focus assay[c)] | Report results only | Negative | Negative | Negative | Negative |
| | Electron microscopy | | Report results only | A-type and C-type retrovirus-like particles observed | A-type and C-type retrovirus-like particles observed | A-type and C-type retrovirus-like particles observed | A-type and C-type retrovirus-like particles observed |
| | Reverse transcriptase | | Report results only | Reverse transcriptase detected | Reverse transcriptase detected | Reverse transcriptase detected | Reverse transcriptase detected |
| Tests for non-endogenous or adventitious viruses | *In vitro* assays | Assay for adventitious viruses[d)] | Negative | Negative | Negative | Negative | Negative |
| | | Bovine virus assay[e)] | Negative | Negative | Negative | Negative | Negative |
| | | Assay for adventitious bovine viruses derived from components other than bovine serum[f)] | Negative | Negative | NT | NT | Negative |
| | *In vivo* assays | Assay to reveal latent viruses[g)] | Negative | Negative | Negative | Negative | Negative |
| | | Assay for mouse thymic virus | Negative | Negative | Negative | Negative | Negative |
| | Mouse antibody production test[h)] | | Negative | Negative | Negative | Negative | Negative |

NT: Not tested

[a)] *Mus dunni* cells were used.

[b)] $MiCl_1$ $S^+L^-$ cells and Mv1Lu mink cells were used.

[c)] SC-1 cells were used.

[d)] MRC-5 cells, Vero cells, HeLa cells, Sp2/0 cells (MCB and WCB), and [redacted] indicator cell line (MCB and CAL) were used.

[e)] Bovine turbinate cells were used and immunostained for bovine adenovirus type 5, bovine parvovirus, bovine viral diarrhea virus, infectious bovine rhinotracheitis virus, and bovine parainfluenza virus type 3.

[f)] Bovine turbinate cells and Vero cells were used.

[g)] Inoculated into adult mice, suckling mice, and guinea pigs, and embryonated eggs.

[h)] polyoma virus, Sendai virus, lymphocytic choriomeningitis virus, ectromelia virus, reovirus type 3, K virus, minute virus of mice, pneumonia virus of mice, mouse hepatitis virus, mouse encephalomyelitis virus, mouse cytomegalovirus, mouse rotavirus, lactic dehydrogenase virus, Hantaan virus, mouse thymic virus, and mouse adenovirus were used. For Lot c of WCB and CAL, mouse parvovirus was also used.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. The MCB is stored at more than one site.

[redacted]

[redacted]. A new WCB will be generated periodically.

### 2.A.(1).3) Manufacturing process

The manufacturing process for the drug substance is as shown below.

| | Manufacturing process | In-process controls |
|---|---|---|
| **Stage 1** | **Preculture and Expansion**<br>Thawing of WCB<br>[redacted]<br>Equipment: culture flasks, culture bags, and [redacted]-L bioreactor | |
| **Stage 2** | **Production Culture**<br>[redacted]<br>Equipment: [redacted]-L production bioreactor | bioburden, mycoplasma, and *in vitro* assay for adventitious viruses |
| **Stage 3** | [redacted] | [redacted] |
| **Stage 4** | **Thawing and pooling of [redacted] eluate** | |
| **Stage 5** | **Solvent/Detergent (S/D) Treatment**<br>[redacted] | [redacted] |
| **Stage 6** | **Cation Exchange Chromatography**<br>Carrier: [redacted] | bioburden and endotoxin |
| **Stage 7** | **Anion Exchange Chromatography**<br>Carrier: [redacted] | bioburden and endotoxin |
| **Stage 8** | **Virus Removal Filtration**<br>Filter: [redacted] | protein concentration, bioburden, and endotoxin |
| **Stage 9** | [redacted] | [redacted] |
| **Stage 10** | **Preparation of ustekinumab formulated bulk (FB)**<br>[redacted]<br>**Ustekinumab FB** | [redacted] |

Note: Critical steps are enclosed in boxes.

[redacted]. The cause of the contamination with *Staphylococcus epidermidis* was identified and then measures were taken to prevent the recurrence.

Table 3. Attributes evaluated in process validation for each stage

| Stages | Attributes evaluated |
|---|---|
| Stage 1 | [redacted] |
| Stage 2 | bioburden, *in vitro* assay for adventitious viruses, and mycoplasma testing (culture method and non-cultural method) |
| Stage 3 | [redacted] |
| Stage 4 | bioburden and endotoxin |
| Stage 5 | [redacted] |
| Stage 6 | [redacted] |
| Stage 7 | [redacted] |
| Stage 8 | [redacted] |
| Stage 9 | [redacted] |
| Stage 10 | [redacted] |

[redacted]

[redacted]

[redacted]

[redacted]

Furthermore, based on the stability evaluation of intermediates produced during the manufacturing process, the storage conditions and storage periods were determined.

**2.A.(1).4) Adventitious agents safety evaluation**

In the manufacturing process for the drug substance, no raw materials of animal origin were used other than Sp2/0 host cells.

Purity tests were performed on the MCB, WCB, and CAL and no viral or non-viral infectious agents were detected other than ERV, and A-type and C-type retrovirus-like particles [see "2.A.(1).2) Characterization and control of cell banks"]. [redacted] batches of culture fluid were evaluated for the presence of retrovirus (assay for ERV[1], $S^+L^-$ focus assay[1], XC plaque assay[1], mink cell focus assay[1], electron microscopy[2]) in process validation and no retrovirus or adventitious virus was detected other

[1] Samples taken from bioreactor on around Day [redacted] or [redacted] of cell culture for productionwere evaluated.

[2] Samples taken from bioreactor on around Days [redacted], [redacted], and [redacted] of cell culture for productionwere evaluated. Note that samples on Day [redacted] instead of samples taken from bioreactor on around Day [redacted] were used for [redacted] of [redacted] batches were evaluated.

than ERV and retrovirus-like particles. In-process testing is performed to ensure that the culture fluid at the end of the production run is free of mycoplasma and adventitious virus contamination.

In order to evaluate the capacity of the purification process to clear viruses, viral clearance studies were performed with relevant viruses and non-specific model viruses as shown in Table 4, which demonstrated that all viruses are adequately removed by the purification process. It has been discussed that the overall reduction factor for ERV indicates that the purification process provides adequate endogenous retrovirus clearance.

Table 4. Results of viral clearance studies

| Manufacturing process | Virus reduction factor ($log_{10}$) (One-sided 95% confidence interval [CI] in parenthesis) | | | |
|---|---|---|---|---|
| | ERV | Poliovirus type 1 | Reovirus type 3 | Pseudorabies virus |
| Stage 3: [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Stage 5: S/D treatment | [redacted] | NT | NT | [redacted] |
| Stage 7: Anion exchange chromatography | [redacted] | [redacted] | [redacted] | [redacted] |
| Stage 8: Viral removal filtration | [redacted] | [redacted] | [redacted] | [redacted] |
| Overall reduction factor | >19.4 (1.0) | ≥6.6 (0.7) | ≥10.5 (0.9) | ≥14.6 (0.8) |

NT: Not tested

### 2.A.(1).5) Manufacturing process development (Comparability)

During the development of ustekinumab, changes were made to the manufacturing process in order to establish a robust manufacturing process for supplying a sufficient quantity of the drug product at an appropriate manufacturing-scale. The major changes are shown in Table 5.

Table 5. Major changes made to the manufacturing process

| Manufacturing method | Manufacturing method A | Manufacturing method B | Manufacturing method C | Manufacturing method D |
|---|---|---|---|---|
| Intended use | Non-clinical studies, Foreign phase I clinical studies | Foreign phase II clinical studies: Psoriasis | Foreign phase II clinical studies: Psoriatic arthritis Multiple sclerosis | Foreign phase III clinical studies Japanese Study JPN-01 Japanese Study JPN-02 To-be-marketed drug product |
| Cell line[a] | B | Same as left | D | Same as left |
| [redacted] | Medium containing bovine-derived raw materials | Same as left | [redacted] | Same as left |
| [redacted] | [redacted]L | [redacted]L | [redacted]L | [redacted]L |
| [redacted] | [redacted] | [redacted] | Same as left | Same as left |
| [redacted] | [redacted] | [redacted] | [redacted] | Same as left |
| Virus removal membrane | [redacted] virus retentive filter | [redacted] virus retentive filter | Same as left | Same as left |
| [redacted] | Of animal origin | Same as left | Of plant origin | Same as left |
| Dosage form | Lyophilized | Same as left | Same as left | Liquid |

a: The cell line B and the cell line D are derived from the same murine myeloma cell line.

[redacted]. The following tests for the comparability exercise were conducted, which demonstrated comparability between the drug substances produced by Manufacturing Methods A and B.

SDS-PAGE, size exclusion chromatography (SE-HPLC), charge heterogeneity (isoelectric focusing [IEF], ion exchange chromatography [IE-HPLC]), potency (a cell-based assay), and process-related impurities (bioburden, endotoxin, residual Protein A, bovine IgG)

For Manufacturing Method C, the cell line and medium etc. were changed. The following tests for the comparability exercise of the drug substances/drug products produced by Manufacturing Methods A and C were conducted.

Peptide mapping, N-terminal amino acid sequencing, circular dichroism spectra (far-ultraviolet, near-ultraviolet), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS), electrospray ionization mass spectrometry (ESI-MS), oligosaccharide mapping, SDS-PAGE, SE-HPLC, charge heterogeneity (IEF, IE-HPLC), potency (a cell-based assay), process-related impurities (HCP, host cell DNA, residual Protein A), degradation profile and degradation rate

[redacted]. Other test results were similar. In addition, a non-clinical study in cynomolgus monkeys showed no differences in pharmacokinetic parameters between products manufactured by method A and C [see "3.(ii) Summary of pharmacokinetic studies"]. These results demonstrated comparability between pre-change and post-change drug substances/drug products.

[redacted].The following tests for the comparability exercise were conducted, which demonstrated comparability between the drug products produced by Manufacturing Methods C and D.

Peptide mapping, N-terminal amino acid sequencing, circular dichroism spectra (far-ultraviolet, near-ultraviolet), differential scanning calorimetry, sedimentation coefficient, ESI-MS, oligosaccharide mapping, SDS-PAGE, SE-HPLC, charge heterogeneity (IEF, IE-HPLC), potency (a cell-based assay), degradation profile and degradation rate, product-related impurities (aggregates, truncated forms), and process-related impurities (HCP, host cell DNA, residual Protein A)

**2.A.(2) Drug substance**

**2.A.(2).1) Structure and composition**

The drug substance has been characterized as follows.

**2.A.(2).1).(a) Primary structure**

● The amino acid sequence of ustekinumab, as determined by N-terminal amino acid sequencing by Edman degradation and peptide mapping, agreed with the one deduced from cDNA.

● Heterogeneity in C-terminal Lys residues of the heavy chain, which is commonly observed in IgG1,

was detected by LC/electrospray ionization quadrupole time-of-flight mass spectrometry (ESI-QTOF MS).

**2.A.(2).1).(b) Higher order structure**

● Two intra-chain disulfide bonds in each light chain, four intra-chain disulfide bonds in each heavy chain, and four inter-chain disulfide bonds (two inter-heavy chain disulfide bonds in the hinge region, one inter-heavy-light chain disulfide bond for each heavy and light chain pair) were identified by peptide mapping under non-reducing conditions. Free sulfhydryl analysis using Ellman's reagent revealed that [redacted]% of all Cys residues are present as free sulfhydryl groups, confirming that almost all Cys residues are involved in disulfide bond formation, as is the case with a typical IgG1.

● [redacted].

● [redacted]

● The sedimentation coefficient as determined by sedimentation velocity analytical ultracentrifugation (SV-AUC) was typical of IgG.

● The apparent molecular weight of ustekinumab, as measured by sedimentation equilibrium AUC, was approximately [redacted], which was close to the molecular weights of different glycoforms of ustekinumab, approximately 148,000 to 150,000, as measured by mass spectrometry, indicating that the molecule is monomeric in solution.

● Differential scanning calorimetry analysis showed that ustekinumab has a folded structure, with a thermally stable conformation.

**2.A.(2).1).(c) Carbohydrate structure**

● Fragment analysis by peptide mapping showed that ustekinumab is glycosylated at Asn299 of the heavy chain.

● Analysis of neutral monosaccharide composition indicated that ustekinumab has a biantennary, core-fucosylated *N*-glycan with galactose heterogeneity. No galactosamine was detected, indicating the absence of *O*-linked glycosylation.

● Oligosaccharide mapping and sequential exoglycosidase digestion revealed that ustekinumab has [redacted] types of biantennary, core-fucosylated glycans with galactose and sialic acid heterogeneity. Neutral oligosaccharides (G0F, [redacted]%; G1F, [redacted]%; G2F, [redacted]%) and sialylated oligosaccharides accounted for [redacted]% and [redacted]%, respectively, of the total glycans.

● The results of sialic acid analysis revealed that [redacted]% of the total sialic acid was *N*-glycolylneuraminic acid (NGNA) and [redacted]% was *N*-acetylneuraminic acid (NANA).

**2.A.(2).1).(d) Isoforms**

● The mass spectrum showed multiple peaks due to the heterogeneity among multiple *N*-glycan structures and partial removal of heavy chain C-terminal Lys. After removing the heavy chain C-terminal Lys residues, the mass spectrum revealed only peaks derived from different *N*-glycans.

● After removing the heavy chain C-terminal Lys residues, both IEF and cIEF profiles revealed [redacted] isoforms in the pI range of [redacted] to [redacted]. Further analyses by IE-HPLC and peptide mapping revealed isoforms with oligosaccharides containing [redacted] to [redacted] sialic acids and those with neutral oligosaccharides.

● The mass spectra of blood samples from the patients treated with ustekinumab produced by the cell line B revealed [redacted] major isoforms. The clearance profiles of these isoforms in the serum over time were similar.

**2.A.(2).1).(e) Other physicochemical properties**

● The extinction coefficient was [redacted] $(mg/mL)^{-1}cm^{-1}$.

**2.A.(2).1).(f) Biological properties**

● Enzyme immunoassay (EIA) and surface plasmon resonance etc. showed that ustekinumab binds specifically to human IL-12 and human IL-23.

● The equilibrium constants for ustekinumab binding to human IL-12 and human IL-23 were [redacted] pmol/L and [redacted] pmol/L, respectively.

● Ustekinumab inhibited human IL-12 and human IL-23 from binding to their receptors (human IL-12Rβ1, human IL-12Rβ1/β2 receptor complex, human IL-12Rβ1/23R receptor complex) by binding to human IL-12/23p40. Ustekinumab could not bind to human IL-12 or human IL-23 that was already bound to their receptors, resulting in no induction of complement dependent cytotoxicity (CDC) [see "3.(i) Summary of pharmacology studies"].

● In an *in vitro* assay using human H cells, ustekinumab was shown to inhibit human IL-12-induced IFN-γ production. In [redacted]-month stability studies at 5°C, [redacted]°C, and [redacted]°C, the activity of ustekinumab decreased over time when stored at [redacted]°C and [redacted]°C, showing that this assay presents the biological properties of ustekinumab for stability evaluation.

● [redacted].

● As to the binding of the Fc region of ustekinumab to [redacted] receptor and [redacted] receptor, the 50% effective concentration (EC50) in [redacted] binding assay was approximately [redacted] ng/mL and the 50% inhibitory concentration (IC50) in [redacted] competitive binding assay was [redacted] to [redacted] μg/mL.

**2.A.(2).2) Product-related substances**

[redacted].

● [redacted].

● Since heavy chain C-terminal Lys residues are removed immediately by enzyme in serum or plasma, the presence or absence of C-terminal Lys residues of the heavy chain is not considered to have an impact on the potency, efficacy, or safety of ustekinumab. Thus, the variants produced due to the loss of C-terminal Lys residue of the heavy chain were considered to be product-related substances.

● [redacted]

**2.A.(2).3) Impurities**

**2.A.(2).3).(a) Process-related impurities**

[redacted]. All the process-related impurities have been demonstrated to be consistently and adequately removed in the manufacturing process [see "2.A.(1).3) Manufacturing process"].

**2.A.(2).3).(b) Product-related impurities**

[redacted]. Based on the results of assessment of the capacity of the manufacturing process to remove impurities, aggregates have been demonstrated to be removed consistently in the manufacturing process [see "2.A.(1).3) Manufacturing process"].

**2.A.(2).4) Drug substance specifications**

[redacted].

**2.A.(2).5) Stability of drug substance**

Using manufacturing-scale batches of drug substance, long-term testing ([redacted]°C [redacted] months, 4 batches; [redacted] months, 3 batches; [redacted] months, 2 batches] and [redacted]°C [redacted] months, 4 batches]), intermediate testing ([redacted]°C [redacted] months, 3 batches; [redacted] months, 2 batches; [redacted] months, 4 batches]), and accelerated testing ([redacted]°C [redacted] months, 9 batches]) were conducted. In all the studies, polycarbonate bottles with polypropylene caps were used to store drug substance samples.

[redacted]

At the long-term storage condition, no changes over time occurred throughout the testing period at either [redacted]°C or [redacted]°C, except for a transient increase in potency at [redacted] months for [redacted] batches stored at [redacted]°C. In the intermediate storage condition ([redacted]°C), [redacted] batches showed a decrease in potency at [redacted] months of storage, but no other changes over time were observed at ≥[redacted] months of storage. No changes over time occurred for other attributes tested.

Based on the above stability data, a shelf life of [redacted] months was proposed for the drug substance when stored at ≤[redacted]°C.

**2.A.(3) Drug product**

**2.A.(3).1) Formulation development**

[redacted]. The proposed product is supplied in a prefilled glass syringe with a stainless needle and each prefilled syringe contains a volume of the drug solution that is sufficient to ensure delivery of 45 mg of ustekinumab. Each prefilled syringe is equipped with a needle safety guard (UltraSafe Passive Delivery System) (needle guard). A carton is used as the secondary packaging.

**2.A.(3).2) Drug product manufacturing process**

The manufacturing process for the drug product is as shown below.

| | Manufacturing process | In-process controls |
|---|---|---|
| **Step 1** | **Thawing of FB** | |
| **Step 2** | **Pooling and Mixing**[1)] | Bioburden and Endotoxin |
| **Step 3** | [redacted] | Bioburden and Endotoxin |
| **Step 4** | **Sterile filtration** [redacted] | Filter integrity |
| **Step 5** | **Filling**[2)] | [redacted] |
| **Step 6** | **Assembly** | |
| **Step 7** | **Secondary packaging** | |
| **Step 8** | **Testing, Storage** | |

1): FB is pooled into the mixer (Step 2) within [redacted] hours after start of thawing (Step 1).
2): Filling is started within [redacted] hours after start of pooling of thawed FB (Step 1) into the mixer (Step 2).
Filling is completed within [redacted] hours.

[redacted]. As a result, the pre-determined acceptance criteria were met for all theattributes evaluated or the quality of the drug product was not affected, showing that the drug product of consistent quality can be manufactured. For

[redacted] batches of another drug product to be supplied in a similar prefilled syringe (with a needle guard), no malfunction of the needle guard fitted in the assembly step was observed. Step [redacted] was defined as a critical step.

**2.A.(3).3) Manufacturing process development**

A liquid formulation for intravenous administration or a lyophilized formulation for subcutaneous administration was used in foreign phase I and phase II clinical studies. Another liquid formulation for subcutaneous administration was used in foreign phase III and Japanese phase I clinical studies. Furthermore, the liquid formulation for subcutaneous administration in a prefilled syringe (the liquid formulation in a prefilled syringe) was used in a Japanese phase II/III study. The liquid formulation in a prefilled syringe equipped with a needle guard is proposed for marketing.

**2.A.(3).4) Drug product specifications**

[redacted]

**2.A.(3).5) Stability of drug product**

Using manufacturing-scale batches of the drug product, long-term testing, accelerated testing, stress testing, photostability testing, and cycle tests were performed. The attributes tested are shown in Table 6.

Table 6. Stability studies on drug product

| | Test conditions | Attributes tested |
|---|---|---|
| Long-term testing | 2°C−8°C (24 months, 5 batches) | [redacted] |
| Accelerated testing | 25°C ([redacted] months, 5 batches) | [redacted] |
| Stress testing | [redacted]°C ([redacted] months, 5 batches) | [redacted] |
| Photostability testing | [redacted]°C, an overall illumination of 1.2 million lux·hr and an integrated near ultraviolet energy of 200 W·h/m$^2$, 1 batch[1)] | [redacted] |
| Cycle tests | Condition 1[2)] and Condition 2[3)], 2 batches each | [redacted] |

[1)] Three types of packaging were used in the study: (a) Primary packaging only (a glass syringe), (b) Primary and Secondary packaging (a carton), (c) Primary and Secondary packaging plus aluminum foil.

[2)] [redacted]

[3)] [redacted]

[redacted].

[redacted].

[redacted]. No significant changes occurred for other attributes tested throughout the testing period.

[redacted]. In the samples of the drug product with primary and secondary packages compared to the samples of the drug product further wrapped with aluminum foil, changes from the initial time point in the IEF pattern were observed, but when a higher-sensitivity method, cIEF, was used, no changes in the cIEF pattern were noted, nor were any changes observed for other attributes tested.

Cycle tests were performed to evaluate the effect of short-term excursions outside the predetermined temperature range during shipping, storage, and use of the product. In the cycle test 1, a slight decrease in potency was observed after [redacted] cycles, but no significant changes were observed for other attributes tested throughout the testing period. In the cycle test 2, no significant changes were observed for the tested attributes throughout the testing period.

Based on the above stability data, a shelf life of 18 months was proposed for the drug product when stored at 2°C to 8°C and protected from light.

**2.A.(4) Reference materials**

[redacted]

[redacted]

[redacted].

## *2.B Outline of the review*

PMDA reviewed the submitted data, including the following major considerations, and concluded that the quality of the product is adequately controlled.

### 2.B.(1) Safety of non-human glycan structures

Non-human glycan structures are present in ustekinumab: sialylated oligosaccharides containing a non-human sialic acid NGNA ([redacted]% of the total glycans) and oligosaccharides containing a non-human Galα1-3Gal. PMDA asked the applicant to explain whether there is a safety concern about administering ustekinumab containing these non-human glycan structures.

The applicant explained as follows:

The glycans of ustekinumab are constrained in the internal cavity enclosed by the two polypeptide backbones of the CH2 domains of the Fc region and sterically shielded so that other molecules have limited access to these glycans. Therefore, these glycans are not considered to be antigenic or immunogenic (Dalziel M, McFarlane I, Axford JS., *Glycoconj J*. 1999;16: 801-7). Based on the clinical experience with ustekinumab in >2000 patients in Japan and overseas, no allergy-related serious adverse events after the initial or repeated doses have been reported and the incidence of anti-ustekinumab antibody development was low, suggesting that oligosaccharides containing NGNA or Galα1-3Gal in ustekinumab are unlikely to be antigenic or immunogenic.

PMDA accepted the above response.

### 2.B.(2) Measures to prevent contamination

During the process validation, 1 batch was found to be contaminated with *Staphylococcus epidermidis* on Day [redacted] of cell culture for production. PMDA asked the applicant to explain the cause of the contamination and the measures to prevent the contamination.

The applicant explained as follows:

It seemed that the contamination was caused by leakage of media after the bioreactor was improperly connected to the media container. As a measure to prevent the contamination, the employees were

retrained on the connecting procedures. Nine batches produced on a commercial manufacturing scale after 2007 were all free of such contamination.

Based on the manufacturing history, PMDA concluded that another contamination of this kind is unlikely to occur in future production and accepted the above response.

**2.B.(3) Drug substance specifications**

PMDA requested the applicant to include in the drug substance specifications a test intended to detect a structural change without charge variation and to directly assess the consistency of the structure of ustekinumab, including heterogeneity due to post-translational modifications etc.

The applicant responded that peptide mapping will be included in the drug substance specifications in order to assure the consistency of the structure of ustekinumab, including heterogeneity.

PMDA accepted the above response.

**2.B.(4) Needle guard fitted to syringe**

PMDA asked the applicant to explain the possibility that the needle guard fitted to the syringe is activated improperly during the use of the product.

The applicant responded as follows:

In foreign countries, no adverse events related to product malfunctions have been reported to date. The following malfunction is most likely to occur: the entire prefilled syringe contents have not been injected and as a result, the needle guard is not activated. However, such a malfunction does not cause adverse events to patients or healthcare providers. An illustrated explanation on how to use the needle guard will be included in the package insert, as a guide to healthcare providers.

PMDA accepted the above response.

**3. Non-clinical data**

**3.(i) Summary of pharmacology studies**

***3.(i).A Summary of the submitted data***

As the primary pharmacodynamic studies of ustekinumab, the binding of ustekinumab to IL-12 and IL-23, inhibition of IL-12 and IL-23 binding to their receptors, inhibition of IL-12 and IL-23 bioactivity, and species binding and neutralization activity were determined. As the reference data, the results from a study using a murine model of psoriasis were submitted. As the secondary pharmacodynamic studies, its effects on asthma and its cross-reactivity with normal human tissues were studied. Although no safety pharmacology studies have been performed, the effects of ustekinumab on the functions listed in the safety pharmacology core battery were investigated based on the data from 26-week and 4-week repeat-dose toxicity studies in cynomolgus monkeys, in

accordance with the ICH guidelines. Ustekinumab derived from the cell line B cultured in medium containing bovine fetal serum was used in pharmacology studies, but, in some studies, ustekinumab derived from the cell line C or ustekinumab derived from the cell line D cultured in serum-free medium were used instead. No pharmacodynamic drug interaction studies have been performed.

**3.(i).A.(1) Primary pharmacodynamics**

**3.(i).A.(1).1) Binding to human IL-12 and IL-23 (4.2.1.1.1)**

**3.(i).A.(1).1).(a) Binding to IL-12, IL-23, and IL-12/23p40**

The binding of ustekinumab to human IL-12, IL-23, or IL-12/23p40 ([redacted] μg/mL) was determined by ELISA. Ustekinumab was shown to have comparable binding to each of IL-12, IL-23, and IL-12/23p40.

n**3.(i).A.(1).1).(b) Binding to proteins related to IL-12/23p40**

**3.(i).A.(1).1).(b) Binding to proteins related to IL-12/23p40**

The binding of ustekinumab to the following proteins was determined by dot blotting: IL-12; IL-12/23p40; IL-6; IL-6 receptor (IL-6sR) and ciliary neurotrophic factor receptor (CNTFR), which are structurally related to IL-12/23p40; and the fusion protein of antibody crystallizable fragment (Fc) and IL-11 receptor, which is functionally related to IL-12/23p40 (IL-11R/Fc). Ustekinumab bound to IL-12 and IL-12/23p40, but not to IL-6, IL-6sR, CNTFR, or IL-11R/Fc.

**3.(i).A.(1).1).(c) Crystal structure analysis**

X-ray crystallographic analysis of ustekinumab Fab/IL-12 complex, formed by the reaction of the antigen-binding fragment (Fab) of ustekinumab with deglycosylated IL-12, showed that the variable domain fragment (Fv) of ustekinumab binds to the epitope in the D1 domain of IL-12/23p40 comprised of three domains (D1-D3), and that the epitope is distant from IL-12p35 (IL-12 consists of IL-12/23p40 and IL-12p35 subunits). The applicant explained that since IL-23p19 overlaps well with IL-12p35 (IL-23 consists of IL-12/23p40 and IL-23p19 subunits) (Beyer BM et al. *J Mol Biol.* 2008;382:942-55), it is believed that also in the case of IL-23, ustekinumab binds to the epitope in the D1 domain of IL-12/23p40 and that the D1 domain is distant from IL-23p19.

**3.(i).A.(1).1).(d) Binding epitope analysis**

The amino acid residues of IL-12/23p40 involved in the binding to ustekinumab were identified by binding epitope analysis, using protein variants with amino acid residues mutated in the D1 domain. Introduction of mutations using site-directed mutagenesis resulted in reduced binding to ustekinumab, indicating that M23, L40, S43, E45, E59, and D62 are the amino acid residues of IL-12/23p40 involved in the binding to ustekinumab.

**3.(i).A.(1).1).(e) Analysis of binding affinity**

The equilibrium constants ($K_D$) for ustekinumab binding to IL-12 and IL-23 as determined by surface plasmon resonance, were [redacted] and [redacted] pmol/L ([redacted] and [redacted] μg/mL), respectively.

**3.(i).A.(1).1).(f) Stoichiometric analysis**

The stoichiometry of ustekinumab binding to IL-12 or IL-23 was conducted by isothermal titration calorimetry. Human IL-12 and IL-23 bound to ustekinumab at ratios of 2:0.94 and 2:0.92, respectively, showing the expected ligand to antibody ratio of 2:1.

**3.(i).A.(1).2) Inhibition of human IL-12 and IL-23 binding to their receptors (4.2.1.1.2)**

**3.(i).A.(1).2).(a) Inhibition of binding to IL-12 receptor β-1 (IL-12Rβ1)**

Human IL-12 or IL-23 ([redacted] ng/mL each) was reacted with ustekinumab ([redacted] ng/mL), which was added to IL-12Rβ1/Fc fusion protein. Ustekinumab demonstrated equivalent inhibition of IL-12 and IL-23 binding to IL-12Rβ1/Fc.

**3.(i).A.(1).2).(b) Inhibition of binding to receptor complexes IL-12Rβ1/β2 and IL-12Rβ1/23R**

Human IL-12 or IL-23 was reacted with ustekinumab or anti-IL-12/23p40 mAb (C8.3) that recognizes a different epitope than ustekinumab and that has no neutralization activity, which was added to the IL-12 responsive cell line (H) or the IL-23 responsive cell line (NKL). Ustekinumab inhibited IL-12 and IL-23 from binding to H cells and NKL cells, respectively, whereas IL-12/23p40 mAb with no neutralization activity did not inhibit IL-12 or IL-23 from binding to the cells.

Based on the above, the applicant explained that ustekinumab was shown to inhibit IL-12 and IL-23 from binding to their receptor complexes expressed on the cell membrane.

**3.(i).A.(1).2).(c) Binding ability to IL-12 and IL-23 already bound to receptors**

Human IL-12 or IL-23 was reacted with H cells or NKL cells and added with ustekinumab or anti-IL-12/23p40 mAb (G) with no neutralization activity. While G was detected on the cell surface, ustekinumab was not detected on the cell surface.

Based on the above, the applicant inferred that ustekinumab cannot bind to IL-12 or IL-23 that is already bound to receptor complexes on the cell surface.

**3.(i).A.(1).2).(d) CDC activity**

Human peripheral blood lymphocytes (PBL) activated by phytohemagglutinin (PHA) were added with human IL-12 and ustekinumab [redacted] μg/mL and treated with complement. Ustekinumab did not induce CDC of PHA-activated PBL.

**3.(i).A.(1).3) Inhibition of IL-12-mediated Th1 cellular response and IL-23-mediated Th17 cellular response (4.2.1.1.3)**

**3.(i).A.(1).3).(a) Effects on intracellular signaling**

The effects of ustekinumab on IL-12-mediated intracellular signaling were determined by flow cytometry. Ustekinumab ([redacted] or [redacted] μg/mL) was reacted with human IL-12 or IL-23 ([redacted] ng/mL each), which was added to NKL cells. Ustekinumab inhibited IL-12-mediated phosphorylation

of signal transducers and activators of transcription STAT4 and STAT6 and IL-23-mediated phosphorylation of STAT3.

**3.(i).A.(1).3).(b) Effects on the expression of cell surface markers**

The effects of ustekinumab on IL-12-mediated expression of cell surface markers were determined by flow cytometry. Human IL-12 ([redacted] ng/mL) was reacted with PHA-activated human peripheral blood mononuclear cells and added with ustekinumab (derived from the cell line B) [redacted] μg/mL. Ustekinumab inhibited the otherwise increased IL-12-mediated expression of IL-12 receptor β-2 (IL-12Rβ2) and cutaneous lymphocyte antigen (CLA).

**3.(i).A.(1).3).(c) Effects on cytokine production**

The effects of ustekinumab on IL-12-mediated cytokine production were determined by ELISA. Ustekinumab (derived from the cell line C) or ustekinumab Fab ([redacted] nmol/L) was reacted with human IL-12 ([redacted] ng/mL), which was added to PHA-activated human T cell blasts. Both ustekinumab and ustekinumab Fab inhibited IFN-γ mRNA expression.

The effects of ustekinumab on IL-23-mediated cytokine production were determined by ELISA. [redacted]

When ustekinumab ([redacted] μg/mL) and human IL-23 ([redacted] ng/mL) were added to NKL cells and incubated in the presence of IL-2 and anti-IFN-γ antibodies, ustekinumab inhibited the production of IL-10.

**3.(i).A.(1).4) Species binding and neutralization activity (4.2.1.1.4)**

**3.(i).A.(1).4).(a) Neutralization activity against IL-12 and IL-23 from different species**

The neutralization activity of ustekinumab against IL-12 and IL-23 from different species was determined by ELISA and RT-PCR. Cytokine-containing culture supernatants prepared from adherent cells in the peripheral blood mononuclear cells or splenocytes from humans, chimpanzees, baboons, cynomolgus monkeys, marmosets, rhesus monkeys, dogs, rabbits, rats, and mice, and serially diluted ustekinumab solutions were added to PHA-activated T cells of the respective species, and IL-12-mediated IFN-γ mRNA expression and IFN-γ protein production and IL-23-mediated IL-17A protein production were used as measures of neutralization activity. Ustekinumab neutralized human, chimpanzee, baboon, cynomolgus monkey, marmoset, and rhesus monkey IL-12, but showed little activity to dog and rabbit IL-12 and no activity to rat and mouse IL-12. Ustekinumab neutralized human, chimpanzee, baboon, cynomolgus monkey, and rhesus monkey IL-23, but showed partial activity to dog IL-23 and no activity to rat and mouse IL-23.

**3.(i).A.(1).4).(b) Binding to and neutralization activity against recombinant cynomolgus monkey IL-12 and IL-23**

Recombinant cynomolgus monkey IL-12 or IL-23 was added with ustekinumab. Ustekinumab was

shown to have comparable binding to human and cynomolgus monkey IL-12 and IL-23. [redacted].

Ustekinumab derived from the cell line C and that from the cell line D were compared for their neutralization activity against recombinant cynomolgus monkey IL-12. They showed comparable inhibition of cynomolgus monkey IL-12 ([redacted] ng/mL)-mediated IFN-γ production from H cells.

**3.(i).A.(1).4).(c) Neutralization activities of anti-mouse IL-12/23p40 antibody and ustekinumab against mouse IL-12 and IL-23**

[redacted].

**3.(i).A.(1).5) Effects in a murine model of psoriasis (Reference data 4.2.1.1.5)**

Psoriasis-like symptoms were induced in severe combined immunodeficiency (SCID) mice (n = 10/group) by intraperitoneal transfer of $CD4^{+}CD45RB^{hi}CD25^{-}$ cells isolated from BALB/cBy mouse splenocytes and 7 and 35 days after the cell transfer, the mice were treated intraperitoneally with 0.5 mg of anti-mouse IL-12/23p40 antibody. Compared to the negative control antibody, anti-mouse IL-12/23p40 antibody significantly reduced the mean severity score, reduced acanthosis and rete ridges (downgrowth to the basal layer), and inhibited inflammatory cell infiltration, and significantly reduced the expression of IL-23p19, IL-1α, IL-6, IL-17A, IL-17F, and IL-22 mRNA and tended to reduce the expression of IFN-γ, TNF-α, and IL-12p35 mRNA in skin tissues.

**3.(i).A.(2) Secondary pharmacodynamics**

**3.(i).A.(2).1) Effects of ustekinumab in a model of asthma in cynomolgus monkeys (a pilot study) (4.2.1.2.2)**

In a model of asthma in cynomolgus monkeys, the effects of IL-12 inhibition by ustekinumab on the exacerbation of asthma were studied. Cynomolgus monkeys (n = 2/group) with positive bronchoconstrictor responses to inhaled *Ascaris suum* antigen were intravenously given ustekinumab (9 or 45 mg/kg) 3 weeks later and then challenged with the antigen 1 hour later. Compared to the changes following the initial antigen challenge before ustekinumab treatment, ustekinumab did not affect pulmonary resistance, dynamic compliance, or cellular composition in bronchoalveolar lavage fluid (BALF). At 4 weeks after the first dose, 1 of the cynomolgus monkeys treated with ustekinumab at 45 mg/kg was given the same dose of ustekinumab followed by antigen challenge in the same manner. As a result, an increased bronchoconstrictor response and an increase in eosinophil count in the BALF were observed.

**3.(i).A.(2).2) Effects of ustekinumab in a model of asthma in cynomolgus monkeys (a confirmatory study) (4.2.1.2.3)**

Cynomolgus monkeys (n = 4/group) with positive bronchoconstrictor responses to *Ascaris suum* antigen were given ustekinumab at 45 mg/kg prior to antigen challenge on two occasions, in the same manner as in the pilot study. Compared to the changes following the initial antigen challenge before ustekinumab treatment, administration of ustekinumab on two occasions did not affect the bronchoconstrictor response or eosinophil count in the BALF following antigen challenge.

**3.(i).A.(2).3) Cross-reactivity with normal human tissues (4.2.1.2.4)**

Using cryosections of normal human tissues[3], cross-reactivity of ustekinumab with normal human tissues was studied by immunohistochemical staining. Ustekinumab did not cross-react with any of the normal human tissues tested.

### *3.(i).B Outline of the review by PMDA*

PMDA asked the applicant to sort out the latest findings on the association between psoriasis and IL-12/IL-23, and the data from non-clinical and clinical studies of ustekinumab, etc. and to discuss in details the mechanism of action of ustekinumab in the treatment of psoriasis.

The applicant explained as follows:

(a) The activation of Th1 and Th17 cells by IL-12 and IL-23, respectively, is believed to play a key role in the development of psoriasis (Nestle FO, Conrad C. *J Invest Dermatol* 2004;123:xiv-xv, Lew W, Bowcock AM, Krueger JG. *Trends Immunol.* 2004;25:295-305, Nickoloff BJ. *Nat Med.* 2007;13:242-4), (b) IL-12 is believed to promote induction of differentiation from $CD4^+$naïve T cells to Th1 cells and activation of natural killer (NK) cells, production of cytokines such as IFN-γ from Th1 and NK cells, and the expression of CLA in inflammatory sites and thereby induces accumulation of T cells in skin lesions of psoriasis and epithelial cell proliferation, leading to the exacerbation of psoriasis (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68), (c) IL-23 induces the production of cytokines such as IL-17 and IL-22 from Th17 cells and these cytokines are believed to induce psoriatic lesions such as epidermal thickening (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68, Zheng Y et al. *Nature.* 2007;445:648-51), (d) Increased expressions of IL-12 and IL-23 genes and proteins in the lesional skin and serum of patients with psoriasis have been reported (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68, Roussaki-Schulze AV et al. *Int J Clin Pharmacol Res*. 2005;xxv:169-73, Chan JR et al. *J Exp Med*. 2006;203:2577-87) and psoriasis therapies such as cyclosporine, narrow-band UVB phototherapy, and anti-TNF therapy have been found to regulate the levels of IL-12 and IL-23 (Torti DC, Feldman SR. *J Am Acad Dermatol*. 2007;57:1059-68), and (e) Single-nucleotide polymorphisms in the IL-12B gene encoding the IL-12/23p40 subunit and the gene encoding the IL-23 receptor subunit have been identified to be associated with psoriasis susceptibility (Cargill M et al. *Am J Hum Genet*. 2007;80:273-90). Taking

[3] Including all normal human tissues as recommended in "Points to Consider in the Manufacture and Testing of Monoclonal Products for Human Use (FDA/CBER)".

account of these findings, IL-12 and IL-23 are considered to play a very important role in the pathogenesis of psoriasis.

As Foreign Study C0379T01 showed that mRNA expression levels of cytokines produced by activated Th1 cells were reduced in psoriatic skin lesions in patients treated with ustekinumab (Toichi E, et al. *J Immunol*. 2006;177:4917-26), it is inferred that the activation of Th1 and Th17 cells is inhibited *in vivo* as well and it is discussed that ustekinumab inhibits the activation of Th1 and Th17 cells by IL-12 and IL-23, respectively, in the psoriatic skin lesions and draining lymph nodes as observed *in vitro* and exerts its therapeutic effects through the reduction of the expression of cytokines, chemokines, and adhesion molecules etc. involved in the pathogenesis of psoriasis.

Based on the submitted data and responses etc., PMDA concluded that the pharmacological effects of ustekinumab via IL-12/23p40 have been demonstrated and that ustekinumab can be expected to be effective in the treatment of psoriasis.

**3.(ii) Summary of pharmacokinetic studies**

***3.(ii).A Summary of the submitted data***

The pharmacokinetics of ustekinumab administered subcutaneously or intravenously were investigated in cynomolgus monkeys. Ustekinumab concentrations in the serum and milk were determined by enzyme-linked immunosorbent assay (ELISA) with human IL-12 adsorbed onto the plate and electrochemiluminescent immunoassay (ECLIA) using monoclonal antibodies against the variable region of ustekinumab (lower limit of quantification, 0.09-0.17 μg/mL [ELISA]; 0.09 μg/mL [ECLIA]), respectively. Anti-ustekinumab antibodies were detemined by ELISA. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean ± standard deviation (SD).

**3.(ii).A.(1) Absorption**

**3.(ii).A.(1).1 Single-dose studies (4.2.2.2.1 to 4.2.2.2.2)**

The pharmacokinetic parameters after a single subcutaneous or intravenous administration of ustekinumab in male cynomolgus monkeys were as shown in Table 7. The bioavailability of subcutaneous ustekinumab was estimated to be ≥90% by comparison of the $AUC_\infty$ values of single-dose subcutaneous and intravenous studies using the same dose of ustekinumab.

Table 7. Pharmacokinetic parameters of ustekinumab after single-dose administration to cynomolgus monkeys

| Dose (mg/kg) | Route | n | $C_{max}$ (μg/mL) | $t_{max}$ (day) | $AUC_\infty$ (μg·day/mL) | $t_{1/2}$ (day) | CL (mL/day/kg) | $Vd_z$ (mL/kg) |
|---|---|---|---|---|---|---|---|---|
| 0.9 | s.c. | 3 | 8.16 ± 1.69 | 3 (3-7) | 131.18 ± 86.00 | 4.71 ± 4.67 | - | - |
| 0.9 | i.v. | 3 | 25.57 ± 5.80 | - | 138.24 ± 27.02 | 7.58 ± 1.68 | 6.7 ± 1.5 | 70.1 ± 19.0 |
| 9 | i.v. | 3 | 436.50 ± 48.36 | - | 2452.50 ± 396.54 | 12.10 ± 1.33 | 3.7 ± 0.6 | 60.4 ± 13.2 |

Mean ± SD except for $t_{max}$, Median (Min-Max) for $t_{max}$, $C_{max}$: maximum serum concentration, $t_{max}$: time to reach the maximum serum concentration,
$AUC_\infty$: area under the serum concentration-time curve from time zero to infinite time, $t_{1/2}$: elimination half-life, CL: total body clearance, $Vd_z$: volume of distribution at the terminal phase

**3.(ii).A.(1).2) Repeat-dose studies (4.2.3.6.1, 4.2.3.5.1.1, 4.2.3.2.1)**

Male and female cynomolgus monkeys (n = 2/sex) were subcutaneously administered 45 mg/kg of ustekinumab twice weekly for 3 weeks. The trough serum concentration of ustekinumab increased with each dose. The $C_{max}$ after the first dose was 349.29 ± 32.51 μg/mL and the $C_{max}$ after the last (the 6th) dose was 2460.02 ± 649.57 μg/mL and ustekinumab was eliminated with a $t_{1/2}$ of 16.31 ± 6.62 days after the last dose.

Male cynomolgus monkeys (n = 6/group) were subcutaneously administered 22.5 or 45 mg/kg of ustekinumab twice weekly for 13 weeks. The $C_{max}$ values after the first dose were 262.57 ± 57.37 and 387.72 ± 111.96 μg/mL, respectively, the $C_{max}$ values after the last (the 26th) dose were 2598.54 ± 702.50 and 3781.85 ± 1322.19 μg/mL, respectively, and ustekinumab was eliminated with a $t_{1/2}$ of 19.88 to 21.93 days (median) after the last dose. The AUCs from time 0 to 91 days after the last dose were 65,174.02 ± 34,807.11 and 86,668.58 ± 37,837.40 μg·day/mL, respectively.

Male and female cynomolgus monkeys (n = 8/sex/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly for 26 weeks. The $C_{max}$ values after the first dose were 370.11 ± 197.51 and 672.64 ± 366.79 μg/mL, respectively, the AUCs from time 0 to 3 days after administration ($AUC_{3day}$) were 765.25 ± 436.75 and 1424.23 ± 700.72 μg·day/mL, respectively, the $C_{max}$ values after the last (the 52nd) dose were 1419.13 ± 493.65 and 2347.08 ± 660.48 μg/mL, respectively, and the $AUC_{3day}$ values were 3660.79 ± 1060.79 and 6185.90 ± 1500.47 μg·day/mL, respectively, and ustekinumab was eliminated with $t_{1/2}$ values of 13.27 ± 4.30 and 11.60 ± 1.95 days, respectively, after the last dose. Trough serum concentrations of ustekinumab were constant after Day 71, which demonstrated that steady-state is reached by Week 13.

The $C_{max}$ and $AUC_{\infty}$ values after a single subcutaneous dose of ustekinumab and after the first dose in a subcutaneous repeat-dose study increased in an almost dose-proportional manner.

The applicant explained about a longer $t_{1/2}$ after multiple-dose administration compared to single-dose administration as follows:

It is inferred that the clearance observed after single-dose administration was accelerated due to the development of anti-ustekinumab antibodies. The $t_{1/2}$ was not substantially different between single- and multiple-dose administrations, and there should be no possibility of higher accumulation of ustekinumab after multiple dosing than predicted from that after single-dose administration.

**3.(ii).A.(1).3) Comparability studies (4.2.2.2.3 to 4.2.2.2.4)**

As two different ustekinumab-producing cell lines (B and D) and two different formulations (liquid and lyophilized formulations) were used during pharmaceutical development, single-dose studies in monkeys were conducted to evaluate the comparability of the pharmacokinetic profile of ustekinumab between batches of material produced by the two different cell lines and between the two different formulations.

Male cynomolgus monkeys (n = 12/group) received a single subcutaneous dose of 9 mg/kg of ustekinumab derived from the cell line B or D. The $C_{max}$ (98.08 ± 22.59 and 82.17 ± 13.75 μg/mL, respectively) and $AUC_{\infty}$ (2377.71 ± 718.07 and 2226.15 ± 688.33 μg·day/mL, respectively) were comparable between the two groups and the $t_{max}$, $t_{1/2}$, CL/F, $Vd_z$/F, and MRT were also comparable.

Male cynomolgus monkeys (n = 15/group) received a single intravenous dose of 4.5 mg/kg of a lyophilized or liquid formulation of ustekinumab and the $C_{max}$ (49.12 ± 24.25 and 45.30 ± 19.74 μg/mL, respectively) and $AUC_{\infty}$ (764.90 ± 233.99 and 792.16 ± 195.94 μg·day/mL, respectively) were comparable between the two groups and the $t_{1/2}$, CL, and $Vd_z$ were also comparable.

**3.(ii).A.(2) Distribution**

No distribution studies of ustekinumab have been conducted because ustekinumab is a fully human IgG monoclonal antibody and generally, cellular uptake of a biological macromolecular drug is not high and the tissue distribution of ustekinumab is considered limited based on its volume of distribution, target proteins, and cross-reactivity with normal human tissues, etc. Fetal transfer studies were conducted using unlabeled ustekinumab.

**3.(ii).A.(2).1) Fetal transfer (4.2.3.5.2.1 to 4.2.3.5.2.2)**

Pregnant cynomolgus monkeys (n = 12/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to gestation day 51. The maternal serum ustekinumab concentrations on gestation days 100 to 102 were 45.24 ± 37.30 and 55.65 ± 16.63 μg/mL, respectively, and the fetal serum ustekinumab concentrations were 16.56 ± 12.32 and 21.56 ± 10.22 μg/mL, respectively.

Pregnant cynomolgus monkeys (n = 12/group) were intravenously given 9 or 45 mg/kg of ustekinumab once weekly from gestation day 20 to gestation day 48. The maternal serum ustekinumab concentrations on gestation day 100 were 19.13 ± 9.47 and 54.47 ± 31.13 μg/mL, respectively, and the fetal serum ustekinumab concentrations were 8.39 ± 4.29 and 19.14 ± 10.64 μg/mL, respectively.

**3.(ii).A.(3) Metabolism and excretion**

No metabolism and excretion studies of ustekinumab have been conducted because ustekinumab is a fully human IgG monoclonal antibody and is degraded into peptides and amino acids and excreted or recycled via pathways in the same manner as endogenous IgG in humans. A study of excretion into milk was conducted.

**3.(ii).A.(3).1) Excretion into milk (4.2.3.5.3.1)**

Pregnant cynomolgus monkeys (n = 20/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to lactation day 33. The ustekinumab concentrations in milk on lactation day 14 (2 days after administration) were 1.43 ± 0.45 and 3.12 ± 1.66 μg/mL,

respectively, and the ustekinumab concentrations in milk on lactation day 28 (2 days after administration) were 1.64 ± 0.48 and 3.18 ± 1.71 μg/mL, respectively.

### *3.(ii).B Outline of the review by PMDA*

PMDA asked the applicant to explain the relationship of IL-12 and IL-23 with the expression of cytochrome p450 (CYP) enzymes.

The applicant explained as follows:
Although there has so far been no report that IL-12/23 affects CYP enzyme expression, some cytokines such as IL-6 and IL-1β have been reported to down-regulate the expression of various CYPs (Abdel-Razzak Z et al. *Mol Pharmacol*. 1993;44: 707-15), and the relationship between IL-12/23 and CYP cannot be denied, nor are there data regarding ustekinumab interactions with drugs that are metabolized by CYP enzymes. Thus, an *in vitro* study to determine the effect of IL-12/23 on CYP enzyme expression is currently ongoing.

PMDA considers as follows:
As it is also envisaged that ustekinumab will be used in combination with CYP substrates such as cyclosporine for the treatment of psoriasis, it is necessary to complete the above study as soon as possible and appropriately provide the obtained information to healthcare providers in clinical settings.

## 3.(iii) Summary of toxicology studies

### *3.(iii).A Summary of the submitted data*

Toxicity studies of ustekinumab conducted were repeat-dose toxicity, reproductive and developmental toxicity, and local tolerance studies. Safety pharmacology endpoints and immunotoxicity measurements were incorporated in the toxicity studies. No anti-ustekinumab antibodies were detected in the animals used in the toxicity studies and ustekinumab exposure has been confirmed to be maintained during the dosing period in all studies.

#### 3.(iii).A.(1) Single-dose toxicity (4.2.2.2.1 to 4.2.2.2.2, 4.2.3.2.1)

No single-dose toxicity studies have been conducted. Single-dose toxicity was evaluated based on the data from single subcutaneous dose and single intravenous dose pharmacokinetic studies in cynomolgus monkeys (4.2.2.2.1 to 4.2.2.2.2) and the data after the first dose in a 26-week subcutaneous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.1). No mortality occurred and no ustekinumab-related effects were observed for clinical observations, body weight, or food consumption up to the high dose of 9 mg/kg in the pharmacokinetic studies and up to the high dose of 45 mg/kg in the 26-week subcutaneous repeat-dose toxicity study (observation after the first dose).

#### 3.(iii).A.(2) Repeat-dose toxicity

As repeat-dose toxicity studies, a 26-week subcutaneous dose toxicity study and a 4-week intravenous dose toxicity study in cynomolgus monkeys were conducted. In the 26-week subcutaneous dose

toxicity study, an animal in the high dose group had diarrhoea, body weight loss, and elevated white blood cell count, etc., which were considered to be associated with bacterial enteritis, were observed and their relationship to ustekinumab could not be denied. The $AUC_{72h}$ and $C_{max}$ of ustekinumab (after the last dose) at the no-observed-adverse-effect level (NOAEL) (45 mg/kg) in the 26-week subcutaneous dose toxicity study in cynomolgus monkeys were approximately 22-fold the $AUC_{\infty}$ after single-dose administration and approximately 116-fold the $C_{max}$ after 4 weeks of once-weekly subcutaneous administration (after the 4th dose) to humans at the maximum recommended clinical dose of 90 mg in a foreign phase II study (Study C0379T04).[4]

**3.(iii).A.(2).1) Twenty-six-week subcutaneous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.1)**

Cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly for 13 or 26 weeks. In this study, as immunological tests, peripheral blood lymphocyte subset analyses ($CD2^+$, $CD3^-$, $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD14^+$, $CD16^+$, $CD20^+$, $CD45^+$) were performed and anti-keyhole limpet hemocyanin (KLH) antibody response was measured following intramuscular injection of KLH in incomplete Freund's adjuvant on Days 14 and 30. One of 16 animals in the 22.5 mg/kg group had ventricular extrasystoles, which were considered coincidental and unrelated to ustekinumab. At Week 26, 1 of 16 animals in the 45 mg/kg group had diarrhoea, body weight loss, and elevated white blood cell count and hyperplasia of the myeloid cells and acute inflammation in the ileum, which were considered to be associated with bacterial enteritis. Although their relationship to inhibition of IL-12 and IL-23 by ustekinumab could not be denied, no findings indicative of immunotoxicity were observed in this animal and immunosuppression by ustekinumab was not suggested in the other dose group or other toxicity studies. Thus, bacterial enteritis may have been coincidental. In the immunological test, peripheral blood lymphocyte subset analyses showed changes in the percentages of $CD45^+$, $CD16^+$, and $CD2^+$ in animals treated with ustekinumab, but these changes were small and were not considered of toxicological significance. KLH analysis showed that anti-KLH antibody titers for male animals in the 45 mg/kg group tended to decrease, which was not considered of toxicological significance because this finding occurred in males only and animal to animal variation in anti-KLH antibody response was observed. The NOAEL was determined to be 45 mg/kg. Safety pharmacology evaluations revealed no ustekinumab-related effects on the cardiovascular, central nervous, or respiratory system.

**3.(iii).A.(2).2) Four-week intravenous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.3)**

Cynomolgus monkeys were intravenously given 0 (saline), 9, or 45 mg/kg of ustekinumab once weekly for 4 weeks. In the 45 mg/kg group, 1 of 10 animals had ventricular extrasystoles and on Day

[4] The AUC or $C_{max}$ of ustekinumab administered at the proposed dosage regimen in Japanese patients with psoriasis was not calculated. The trough concentration at the NOAEL (45 mg/kg) in a 26-week subcutaneous dose toxicity study in cynomolgus monkeys after the last dose (Day 166) was 531-fold (maximum) or 2125-fold (median) the trough concentration at Week 64 in Japanese patients with psoriasis administered ustekinumab at the maximum recommended clinical dose of 90 mg at Weeks 0 and 4 and then every 12 weeks (Study JPN-02).

28 (6 days after the 4th dose), compared to the control group, its relative lymphocyte counts decreased and its absolute and relative neutrophil counts increased. The ventricular extrasystoles were considered coincidental and unrelated to ustekinumab. When the lymphocyte and neutrophil values, etc., were compared with their pre-dose values, only 1 of the 10 animals showed a marked decrease in relative lymphocyte counts and a marked increase in relative neutrophil counts, and lymphocyte and neutrophil values for the other animals were almost unchanged from their pre-dose values. The lymphocytes or neutrophils on Days 9 and 58 were unaffected and moreover, no changes were observed in males. Therefore, these changes were not considered of toxicological significance. There were no ustekinumab-related effects on other parameters including immunotoxicity endpoints. The NOAEL in this study was determined to be 45 mg/kg. Safety pharmacology evaluations revealed no ustekinumab-related effects on the cardiovascular, central nervous, or respiratory system.

**3.(iii).A.(3) Genotoxicity**

Since ustekinumab is an antibody drug and there should be little concern about genotoxicity, no genotoxicity studies have been conducted.

**3.(iii).A.(4) Carcinogenicity**

Ustekinumab does not neutralize IL-12 or IL-23 from mice or rats, which are commonly used in carcinogenicity studies, and although anti-mouse IL-12/23p40 antibody (CNTO 3913), an antibody analogous to ustekinumab, neutralizes mouse IL-12 and IL-23, the information to be obtained from a carcinogenicity study with CNTO 3913 should be limited. Therefore, no carcinogenicity studies using ustekinumab or the antibody analogous to ustekinumab have been performed.

**3.(iii).A.(5) Reproductive and developmental toxicity**

A male fertility study in cynomolgus monkeys, a female fertility study with an analogous antibody CNTO 3913 in mice, an embryo-fetal development study in cynomolgus monkeys, and a study for effects on pre- and postnatal development including maternal function in cynomolgus monkeys were conducted by the subcutaneous route of administration. An embryo-fetal development study in cynomolgus monkeys was conducted by the intravenous route of administration. Ustekinumab was not teratogenic and there were no effects on either male or female fertility, parturition, embryo-fetal development, or offspring development in any of the studies. Ustekinumab has been shown to cross the placenta (4.2.3.5.2.1) and be excreted in milk (4.2.3.5.3.1) in cynomolgus monkeys [see "3.(ii).A.(2).1) and 3.(ii).A.(3).1)"].

**3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation**

The levels of IL-12 in seminal plasma of infertile men were lower than those of fertile men and there was significant correlation between the IL-12 levels and the total sperm count and percentage of morphologically normal sperm in the semen (Naz RK et al. *J Androl*. 1998;19:302-307). Thus, a male fertility study in cynomolgus monkeys was conducted.

**3.(iii).A.(5).1).(a) Male fertility study in cynomolgus monkeys (4.2.3.5.1.1)**

Male cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly for 13 weeks (9 weeks prior to mating and 4 weeks of mating period). There were no ustekinumab-related effects on clinical observations, body weight and food consumption, semen analysis, mating behavior, or serum testosterone and inhibin B levels. No anti-ustekinumab antibodies were detected. The NOAEL for general and reproductive toxicity was determined to be 45 mg/kg.

**3.(iii).A.(5).1).(b) Female fertility study with CNTO 3913 in mice (4.2.3.5.1.2)**

Female mice were subcutaneously administered 0 (phosphate-buffered saline), 5, or 50 mg/kg of CNTO 3913 (anti-mouse IL-12/23p40 antibody) or 50 mg/kg of an isotype-matched control monoclonal antibody (CNTO 1322) as the negative control article of CNTO 3913, twice weekly beginning 15 days before mating and continuing through gestation day 7. Cesarean section was performed on gestation day 13 and female fertility was evaluated. Although 1 of 25 dams in the CNTO 3913 50 mg/kg group had total litter loss, as the litter average for nonviable embryos in the CNTO 3913 50 mg/kg group (0.3) was lower than those in the vehicle control (0.8) and negative control article (0.7) groups, the finding was not considered related to CNTO 3913. The NOAEL for general and reproductive toxicity was determined to be 50 mg/kg.

**3.(iii).A.(5).2) Embryo-fetal development studies**

**3.(iii).A.(5).2).(a) Subcutaneous administration study in cynomolgus monkeys (4.2.3.5.2.1)**

Pregnant cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to gestation day 51. Hormone concentrations in maternal and fetal serum were measured and as immunological tests, maternal and fetal peripheral blood lymphocyte subset analyses and immunohistochemical analysis of fetal lymphoid tissue were performed. Abortion occurred in 1 of 12 dams in the control group, abortion occurred in 3 of 12 dams and embryo/fetal death occurred in 2 of 12 dams in the 22.5 mg/kg group, and embryo/fetal death occurred in 2 of 12 dams in the 45 mg/kg group. Although the incidence of abortion or embryo/fetal death in the 22.5 mg/kg group (5 of 12 dams, 41.7%) exceeded the laboratory historical control range (mean 8.2%, maximum 20%), the incidence in the 45 mg/kg group (2 of 12 dams, 16.7%) was within the historical control range and no dose-dependency was observed. Abortion or embryo/fetal death did not necessarily occur in animals with high ustekinumab exposure levels. There was no correlation between individual exposure levels and abortion or embryo/fetal death. In addition, an embryo-fetal development study in cynomolgus monkeys by intravenous administration (4.2.3.5.2.2) showed that the incidence of abortion or embryo/fetal death in animals treated with ustekinumab was within the historical control range. Therefore, the findings were not considered related to ustekinumab. Although statistically significant differences between the ustekinumab and control groups were observed for serum hormone concentrations (progesterone, 17β-estradiol, prolactin), these changes were within the laboratory historical control range or transient. There was no relationship between changes in serum hormone concentrations and abortion or embryo/fetal death, and maintenance of pregnancy was not affected. Therefore, these changes were not considered related to ustekinumab.

Asymmetrically aligned palatal rugae were observed in 1 of 7 fetuses in the 22.5 mg/kg group and 1 of 10 fetuses in the 45 mg/kg group, but were not reported in a study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1) and morphological changes in the palate are commonly observed in adult cynomolgus monkeys and are not associated with dysfunction. Thus, this finding was not considered of toxicological significance. No anti-ustekinumab antibodies were detected in maternal or fetal serum. The NOAEL for maternal and embryo-fetal toxicity was determined to be 45 mg/kg.

**3.(iii).A.(5).2).(b) Intravenous administration study in cynomolgus monkeys (4.2.3.5.2.2)**

Pregnant cynomolgus monkeys were intravenously given 0 (saline), 9, or 45 mg/kg of ustekinumab once weekly from gestation day 20 to gestation day 48. As immunological tests, maternal and fetal peripheral blood lymphocyte subset analyses and immunohistochemical analysis of fetal lymphoid tissue were also performed. Abortion occurred in 1 of 12 dams each in the 9 mg/kg and 45 mg/kg groups, which was not considered related to ustekinumab because abortion occurred in 1 of 12 dams and embryo/fetal death occurred in 1 of 12 dams also in the control group and the incidence was within the laboratory historical control range (mean 8.2%, maximum 20%), etc.

Asymmetrically aligned palatal rugae were observed in 1 of 11 fetuses in the 9 mg/kg group, but not in the 45 mg/kg group, showing no dose-dependency and this finding was not reported in a study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1) and morphological changes in the palate are commonly observed in adult cynomolgus monkeys and are not associated with dysfunction. Thus, the finding was not considered of toxicological significance. No anti-ustekinumab antibodies were detected in maternal or fetal serum. The NOAEL for maternal and embryo-fetal toxicity was determined to be 45 mg/kg.

**3.(iii).A.(5).3) Study for effects on pre- and postnatal development, including maternal function in cynomolgus monkeys (4.2.3.5.3.1)**

Pregnant cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly from gestation day 20 through Day 33 after delivery. In the F1 generation, as immunological tests, peripheral blood lymphocyte subset analyses were performed and immunological development was evaluated (measurement of anti-KLH and anti-tetanus toxoid antibodies). In the 22.5 mg/kg group, abortion occurred in 3 of 20 dams, stillbirth occurred in 2 of 20 dams, and fetal death occurred in 1 of 20 dams. In the 45 mg/kg group, abortion occurred in 3 of 20 dams, stillbirth occurred in 1 of 20 dams, and fetal death occurred in 1 of 20 dams. Also in the control group, abortion occurred in 2 of 20 dams and stillbirth occurred in 3 of 20 dams. As there were no differences in incidence between the control and ustekinumab groups, the findings were not considered related to ustekinumab. Necropsies of the stillbirths revealed no macroscopic abnormalities. In the F1 generation, 1 of 16 animals in the 22.5 mg/kg group died on postnatal day 6 and this animal had low body weight, emaciation, and smaller thymus with an almost empty gastrointestinal tract, but

no death occurred in the 45 mg/kg group and the incidence of neonatal deaths was within the laboratory historical control range (3.7%). Thus, the death was not considered related to ustekinumab. Although 1 of 16 F1 animals in the 45 mg/kg group was sacrificed moribund on Day 1 after birth due to lateral position and the fingertips bitten off by the dam, the tip of the tail of 1 of 18 F1 animals was bitten off by the dam on Day 17 after birth also in the control group. Thus, the finding was not considered related to ustekinumab. In the F1 generation, there were no ustekinumab-related effects including those on immunological test results. In the ustekinumab groups, ustekinumab was present in the offspring and in the breast milk from lactating dams. No anti-ustekinumab antibodies were detected in maternal or offspring serum. The NOAEL for maternal and offspring toxicity was determined to be 45 mg/kg.

**3.(iii).A.(6) Local tolerance study in cynomolgus monkeys (4.2.3.6.1)**

Cynomolgus monkeys were subcutaneously given 0 (vehicle, [redacted]% sucrose, [redacted]% mol/L sodium phosphate, [redacted]% polysorbate 80) or 45 mg/kg of ustekinumab or 3 mg/kg of intravenous immunoglobulin (IGIV) as the positive control article, twice weekly for 3 weeks. Animals in the ustekinumab and vehicle control groups had minimal to mild edema at the injection site, which resolved within 48 hours after injection and no histopathological findings were observed. It was concluded that local tolerance of subcutaneous injection of ustekinumab is good.

## *3.(iii).B Outline of the review by PMDA*

**3.(iii).B.(1) Carcinogenicity**

PMDA asked the applicant to explain the carcinogenic risk of ustekinumab and the risk of exacerbation of malignancy.

The applicant explained as follows:

No tumors or preneoplastic lesions were observed in a 26-week subcutaneous dose toxicity study in cynomolgus monkeys (4.2.3.2.1), suggesting no risk of malignancy development with ustekinumab. As for IL-12/23p40, the target molecule of ustekinumab, however, the anti-tumor effect of IL-12 in laboratory animals has been suggested (Brunda MJ et al. *J Exp Med.* 1993;178:1223-1230, Lee JC et al. *Cancer Res.* 2002;62:747-755) and studies using knockout mice and anti-IL-12/23p40 antibody have suggested the exacerbation of malignancy (Langowski JL et al. *Nature.* 2006;442:461-465). Concerning the risk of photocarcinogenicity, there is a report suggesting the exacerbation of UV-induced skin tumors in IL-12/23p40 knockout mice (Maeda A et al. *Cancer Res.* 2006;66:2962-2969). In addition, the possibility that other immunosuppressive biologics and immunosuppressants are associated with the development of malignancies such as lymphoma in a clinical setting cannot be denied. Taking account of these findings, the risk of malignancy development with ustekinumab also cannot be denied.

**3.(iii).B.(2) Risk of immunosuppression**

Concerning the findings considered to be associated with bacterial enteritis observed in 1 of 16 cynomolgus monkeys in the 45 mg/kg group in a 26-week toxicity study (4.2.3.2.1), PMDA asked the applicant to explain their relationship to the immunosuppressive effect of ustekinumab and the risk of infections associated with ustekinumab in humans.

The applicant explained as follows:

Although this animal had inflammatory response, immunohistochemical analysis of lymphoid tissue and peripheral blood lymphocyte subset analyses revealed no findings indicative of immunotoxicity and T-cell dependent anti-KLH antibody response was not affected either. Therefore, the applicant considered that there were no effects on the immune function and that an increased susceptibility to infections was not suggested. Moreover, in repeat-dose toxicity (4.2.3.2.1 and 4.2.3.2.3) and reproductive and developmental toxicity (4.2.3.5.2.1 to 4.2.3.5.2.2) studies in cynomolgus monkeys, the results of immunotoxicity evaluations showed that ustekinumab was not associated with immunosuppression and naturally occurring diarrhoea is often observed in cynomolgus monkeys in the control group or during acclimatization as well (Trib GW et al. *Lab Anim*. 1983;17:65-69). Taking account of these findings, bacterial enteritis may have been coincidental and although its relationship to ustekinumab cannot be denied, it is very unlikely to be related to the immunosuppressive effect of ustekinumab.

In patients genetically deficient in factors involved in Th1/Th17 cell activation, such as IL-12/23p40, IL-12Rβ1, IFN-γ receptors 1 and 2, STAT1, and NEMO (NF-κB essential modulator), an increased susceptibility to initial mycobacterial infection and recurrent *Salmonella* infection has been reported (Novelli F et al. *Cytokine Growth Factor Rev.* 2004;15:367-377, Fieschi C et al. *J Exp Med*. 2003;197:527-535, Fieschi C, Casanova JL. *Eur J Immunol*, 2003;33:1461-1464, Filipe-Santos O et al. *Semin Immunol,* 2006;18:347-361), while reports of other infections are limited. Thus, it is inferred that protective immunity against most microorganisms is maintained during treatment with ustekinumab. However, as serious infections have been reported in Japanese and foreign clinical studies [see "4.(ii) Summary of clinical efficacy and safety"], the risk of infections associated with ustekinumab cannot be denied, as in the case of other immunosuppressive biologics.

**3.(iii).B.(3) Cardiac effects**

Ventricular extrasystoles were observed in 26-week and 4-week toxicity studies in cynomolgus monkeys (4.2.3.2.1 and 4.2.3.2.3). PMDA asked the applicant to explain its relationship to ustekinumab.

The applicant explained as follows:

It has been reported that ventricular extrasystoles were observed in ECG from 5 of 62 normal cynomolgus monkeys (8%) (Medcallum GE et al. *Am J Vet Res.* 1993;54:327-332) and according to reports on ECGs recorded in cynomolgus monkey toxicity studies (Detweiler DK,

Electrocardiography in toxicology studies. In: Sipes IG, McQueen CA, Gandolfi AJ ed. *Comprehensive toxicology,* UK: Elsevier Science; 1997;95-115), the incidence of arrhythmia and conductance abnormalities in cynomolgus monkeys (n = 4822) was 2.43% (ventricular extrasystoles, 1.24%; right bundle branch block, 1.12%) and compared to these data, the incidence of ventricular extrasystoles in the ustekinumab toxicity studies was not markedly higher. Furthermore, histopathological examination revealed no toxicological findings in cardiac tissue in these toxicity studies, and in a study of cross-reactivity with normal human tissues (4.2.1.2.4), ustekinumab binding to cardiac tissue was not observed and ustekinumab is not thought to induce antibody or CDC of cardiac cells. Therefore, the ventricular extrasystoles observed in these toxicity studies are not considered related to ustekinumab.

PMDA largely accepts the above responses from a toxicological point of view, but considers that the risk of carcinogenicity and infections due to immunosuppression cannot be denied in view of the pharmacological effects of ustekinumab and it is necessary to carefully assess the safety of ustekinumab in clinical use based on clinical study data and post-marketing data etc.

**4. Clinical data**

**4.(i) Summary of clinical pharmacology studies**

***4.(i).A Summary of the submitted data***

As the evaluation data on the pharmacokinetics of ustekinumab, the results from a phase I clinical study in Japanese patients with psoriasis (5.3.3.2.1) and a phase II/III clinical study in Japanese patients with psoriasis (5.3.5.1.2-1) and phase I clinical studies in foreign patients with psoriasis (5.3.3.2.2, 5.3.3.2.3), a phase II clinical study in foreign patients with psoriasis (5.3.5.1.1), and phase III clinical studies in foreign patients with psoriasis (5.3.5.1.3-1 to 5.3.5.1.3-3, 5.3.5.1.4-1 to 5.3.5.1.4-3) and population pharmacokinetic analyses (5.3.3.5.1 to 5.3.3.5.2) and a study of ethnic differences (5.3.3.3.1) etc. were submitted. As the reference data, the results of an analysis of correlation between serum ustekinumab concentration and efficacy in foreign patients with psoriasis (5.3.5.3.1) etc. were submitted. Serum ustekinumab concentrations were determined by an ELISA with human IL-12 adsorbed onto the plate (lower limit of quantification, 0.08 μg/mL) or an ECLIA using monoclonal antibodies against the variable region of ustekinumab (lower limit of quantification, 16.88 ng/mL). Anti-ustekinumab antibodies were measured by an enzyme immunoassay (EIA) and neutralizing antibodies were measured by human IL-12-induced IFN-γ production by NK cells. Unless otherwise specified, the data and pharmacokinetic parameters are expressed as the mean or the mean ± SD.

**4.(i).A.(1) Pharmacokinetics in patients with psoriasis**

***Japanese clinical studies***

**4.(i).A.(1).1) Single subcutaneous administration study (5.3.3.2.1, Study JNS009-JPN-01 [February 2006 to March 2007])**

A placebo-controlled, randomized, double-blind study was conducted in Japanese patients with psoriasis vulgaris (n = 24, 64.89 ± 9.90 kg). The pharmacokinetic parameters following a single subcutaneous administration of 22.5, 45, or 90 mg of ustekinumab were as shown in Table 8. The increase in $C_{max}$ tended to be more than dose-proportional at doses up to 90 mg and was dose-proportional between doses of 22.5 mg and 45 mg. The $AUC_{\infty}$ increased in a dose-proportional manner and the $t_{1/2}$ was almost constant, regardless of dose.

Table 8. Pharmacokinetic parameters following a single subcutaneous administration of ustekinumab to Japanese patients with psoriasis vulgaris

| Dose | $C_{max}$ (μg/mL) | $AUC_{0\text{-}84day}$ (μg.day/mL) | $AUC_{\infty}$ (μg.day/mL) | $t_{max}$ (day) | $t_{1/2}$ (day) | CL/F (mL/day) | Vz/F (L) |
|---|---|---|---|---|---|---|---|
| 22.5 mg | 1.412 ± 0.380 | 49.93 ± 11.04 | 70.59 ± 32.29 | 6.99 (4.0-27.0) | 53.48 ± 79.19 | 364.49 ± 126.50 | 18.84 ± 17.04 |
| 45 mg | 3.034 ± 0.636 | 105.30 ± 34.95 | 139.87 ± 80.14 | 10.48 (4.0-14.00) | 39.07 ± 41.88 | 451.29 ± 195.23 | 18.23 ± 6.82 |
| 90 mg | 8.507 ± 2.397 | 222.80 ± 72.67 | 242.97 ± 78.45 | 10.49 (4.0-14.00) | 24.38 ± 8.30 | 385.15 ± 170.79 | 14.41 ± 11.54 |

Mean ± SD, Median (Min-Max) for $t_{max}$

**4.(i).A.(1).2) Multiple subcutaneous administration study (5.3.5.1.2-1 to 5.3.5.1.2-2, Study JNS009-JPN-02 [March 2008 to March 2010])**

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in Japanese patients with plaque psoriasis (n = 158, 71.95 ± 14.00 kg). When 45 and 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks, at each sampling timepoint from Week 4 through Week 64, serum ustekinumab concentrations were almost dose-proportional and the trough serum concentrations of ustekinumab (median)[5] were 0.25 and 0.74 μg/mL, respectively, at Week 16, 0.25 and 0.65 μg/mL, respectively, at Week 28, 0.28 and 0.55 μg/mL, respectively, at Week 40, 0.29 and 0.67 μg/mL, respectively, at Week 52, and 0.31 and 0.76 μg/mL, respectively, at Week 64 and it was considered that the steady-state serum concentrations of ustekinumab were achieved by Week 28.

***Foreign clinical studies***

**4.(i).A.(1).3) Single intravenous administration study (5.3.3.2.2, Study C0379T01 [April 2001 to August 2002])**

An open-label, single ascending dose study was conducted in foreign patients with psoriasis vulgaris (n = 18, 92.98 ± 23.71 kg). The pharmacokinetic parameters following single ascending intravenous administrations of 0.09, 0.27, 0.9, and 4.5 mg/kg of ustekinumab were as shown in Table 9. $C_{max}$ was reached immediately after intravenous infusion and then ustekinumab was eliminated biphasically until Week 16. The $C_{max}$ and $AUC_{\infty}$ were dose-proportional over the dose range studied and the CL and $Vd_z$ were constant, regardless of dose. The $Vd_z$ was similar to the blood volume.

Table 9. Pharmacokinetic parameters following a single intravenous administration of ustekinumab to foreign patients with psoriasis vulgaris

| Dose | $C_{max}$ (μg/mL) | $AUC_{\infty}$ (μg.day/mL) | $t_{1/2}$ (day) | CL (mL/day/kg) | $Vd_z$ (mL/kg) |
|---|---|---|---|---|---|
| 0.09 mg/kg | 2.7 ± 0.5 | 48.2 ± 8.0 | 27.0 ± 7.5 | 1.90 ± 0.28 | 74.5 ± 24.1 |
| 0.27 mg/kg | 8.9 ± 1.6 | 127.6 ± 14.3 | 18.5 ± 3.6 | 2.14 ± 0.26 | 56.1 ± 6.5 |
| 0.9 mg/kg | 25.5 ± 7.2 | 434.7 ± 133.3 | 25.9 ± 3.7 | 2.22 ± 0.63 | 82.1 ± 23.6 |
| 4.5 mg/kg | 136.8 ± 17.2 | 2346.8 ± 359.0 | 23.7 ± 5.7 | 1.96 ± 0.34 | 66.2 ± 15.4 |

Mean ± SD

[5] Data through Week 64 from subjects subcutaneously treated with ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 58-64 subjects; 90 mg group, 53-62 subjects; the placebo group was not included.)

**4.(i).A.(1).4) Single subcutaneous administration study (5.3.3.2.3, Study C0379T02 [June 2002 to May 2003])**

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with psoriasis vulgaris (n = 21, 96.4 ± 14.0 kg). The pharmacokinetic parameters following a single subcutaneous administration of 0.27, 0.675, 1.35, or 2.7 mg/kg of ustekinumab were as shown in Table 10. The $C_{max}$ and $AUC_{\infty}$ increased in an almost dose-proportional manner over the dose range studied. The $t_{1/2}$ slightly increased dose-dependently though an adequate assessment was difficult for the low-dose group. The absolute bioavailability calculated from $AUC_{\infty}$ values after intravenous (Study T01) and subcutaneous (Study T02) administration was approximately 57.2%.

Table 10. Pharmacokinetic parameters following a single subcutaneous administration of ustekinumab to foreign patients with psoriasis vulgaris

| Dose | $C_{max}$ (μg/mL) | $AUC_{\infty}$ (μg.day/mL) | $t_{max}$ (day) | $t_{1/2}$ (day) | F* (%) | CL/F (mL/day/kg) | Vz/F (mL/kg) |
|---|---|---|---|---|---|---|---|
| 0.27 mg/kg | 3.08 ± 1.70 | 90.8 ± 35.8 | 14.2 (7.1-15.1) | 14.9 ± 4.6 | 67.9 ± 26.6 | 3.43 ± 1.65 | 72.8 ± 34.2 |
| 0.675 mg/kg | 5.22 ± 2.58 | 169.7 ± 39.4 | 14.0 (4.0-14.3) | 17.3 ± 2.5 | 49.3 ± 11.1 | 4.20 ± 0.95 | 106.1 ± 34.9 |
| 1.35 mg/kg | 7.21 ± 2.39 | 323.1 ± 86.7 | 10.7 (7.0-14.2) | 21.2 ± 3.6 | 47.9 ± 12.6 | 4.34 ± 0.95 | 131.1 ± 29.2 |
| 2.7 mg/kg | 14.10 ± 2.82 | 832.3 ± 390.0 | 14.0 (7.1-14.1) | 28.6 ± 9.3 | 61.4 ± 28.8 | 4.17 ± 2.75 | 144.4 ± 33.7 |

Mean ± SD, Median (Min-Max) for $t_{max}$ *: Calculated as the ratio of $AUC_{\infty}$ after subcutaneous administration (Study T02) to $AUC_{\infty}$ after intravenous administration (Study T01)

**4.(i).A.(1).5) Single or multiple subcutaneous administration study (5.3.5.1.1, Study C0379T04 [June 2003 to March 2005])**

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 320, 93.0 ± 22.7 kg). The pharmacokinetic parameters following a single subcutaneous administration or 4 weekly subcutaneous administrations of 45 or 90 mg of ustekinumab were as shown in Table 11 (Pharmacokinetic analysis population, 110 subjects). The $t_{1/2}$ following 4 weekly administrations of ustekinumab was similar to that following a single subcutaneous administration of ustekinumab.

Table 11. Pharmacokinetic parameters following a single subcutaneous administration or 4 weekly subcutaneous administrations of ustekinumab to foreign patients with psoriasis vulgaris

| Dose | | $C_{max}$ (μg/mL) | $AUC_{\infty}$ (μg.day/mL) | $t_{max}$ (day) | $t_{1/2}$ (day) |
|---|---|---|---|---|---|
| Single dose | 45 mg | 2.7 ± 1.2 | 196.7 ± 298.2 | 13.5 (1.9-58.2) | 45.6 ± 80.2 |
| | 90 mg | 6.1 ± 3.6 | 274.9 ± 206.5 | 7.0 (2.9-27.1) | 26.7 ± 19.3 |
| Multiple doses | 45 mg | 13.6 ± 5.7 | - | 3.0 (0.9-35.0) | 24.9 ± 7.9 |
| | 90 mg | 22.9 ± 13.1 | - | 3.0 (0.9-14.0) | 28.1 ± 7.3 |

Mean ± SD, Median (Min-Max) for $t_{max}$

**4.(i).A.(1).6) Multiple subcutaneous administration study (5.3.5.1.3-1 to 5.3.5.1.3-3, Study C0743T08 [December 2005 to ongoing (data cut-off of March 2009)])**

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 766, 93.88 ± 23.69 kg), to whom 45 or 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks. At each sampling timepoint from Week 4 through Week 28, serum ustekinumab concentrations were almost dose-proportional and the trough serum concentrations of ustekinumab (median)[6] in the 45 and 90 mg

[6] Data through Week 28 were obtained from subjects subcutaneously administered ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 242-253 subjects; 90 mg group, 236-253 subjects; the placebo group was not included.). Data at and after Week 52 were obtained from subjects who were re-randomized to receive dosing every 12 weeks at Week 40 (45 mg group, 52-75 subjects; 90 mg group,

groups were 0.25 and 0.49 μg/mL, respectively, at Week 16; 0.21 and 0.47 μg/mL, respectively, at Week 28; 0.26 and 0.58 μg/mL, respectively, at Week 52; 0.50 and 0.89 μg/mL, respectively, at Week 88; 0.49 and 0.88 μg/mL, respectively, at Week 112; and 0.44 and 1.08 μg/mL, respectively, at Week 148.

**4.(i).A.(1).7) Multiple subcutaneous administration study (5.3.5.1.4-1 to 5.3.5.1.4-3, Study C0743T09 [March 2006 to ongoing (data cut-off of August 2008)])**

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 1230, 90.99 ± 21.28 kg). When 45 or 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks, serum ustekinumab concentrations were dose-proportional and the trough serum concentrations of ustekinumab (median)[7] in the 45 and 90 mg groups were 0.37 and 0.65 μg/mL, respectively, at Week 16; 0.34 and 0.56 μg/mL, respectively, at Week 28; 0.36 and 0.64 μg/mL, respectively, at Week 40; and 0.40 and 0.68 μg/mL, respectively, at Week 52. The steady-state serum concentrations of ustekinumab were considered to be achieved by Week 28. When 45 or 90 mg of ustekinumab were subcutaneously administered every 8 weeks beginning at Week 28, the trough serum concentrations of ustekinumab (median) at Week 52 were 3.4-fold and 2.5-fold higher, respectively, than those following dosing every 12 weeks. The liquid in vial formulation (LIV formulation) was switched to the liquid in prefilled syringe formulation (PFS formulation) at Week 52 for a long-term extension period and the trough serum concentrations of ustekinumab (median)[8] after administration of 45 and 90 mg of ustekinumab every 12 weeks were similar between the two formulations, i.e. 0.38 and 0.68 μg/mL, respectively, at Week 40 and 0.40 and 0.72 μg/mL, respectively, at Week 52 for the LIV formulation and 0.42 and 0.73 μg/mL, respectively, at Week 88 for the PFS formulation.

**4.(i).A.(2) Population pharmacokinetic analysis**

**4.(i).A.(2).1) Population pharmacokinetic (PPK) analysis using the data from clinical studies in foreign patients with psoriasis (5.3.3.5.1)**

Using the serum ustekinumab concentration data from a total of 1937 subjects (9938 sampling points) in phase III studies in foreign patients with psoriasis (Studies T08 and T09), PPK analysis was performed using non-linear mixed effect modeling (NONMEM). A one-compartment model with first-order absorption was used as a base model to build up a final model. The CL/F and Vd/F values for ustekinumab estimated from the final model were 0.465 L/day and 15.7 L, respectively. Factors that could contribute to the variability in CL/F and Vd/F were identified. Body weight, diabetes comorbidity, positive immune response to ustekinumab, albumin, creatinine clearance, gender, and

59-84 subjects). The applicant explained that at and after Week 88, higher values were obtained because the assay method was changed from ECLIA-BV to ECLIA-MSD.

[7] Data from subjects subcutaneously administered ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 243-249 subjects; 90 mg group, 279-285 subjects). Subjects in the placebo group or subjects who failed to achieve a PASI 75 response or who were adjusted to dosing every 8 weeks at Week 28 were not included.

[8] Data from subjects who achieved a PASI 75 response at Weeks 28 and 40 and continued dosing every 12 weeks and received the PFS formulation during the long-term extension period after Week 52 (45 mg group, 206-211 subjects; 90 mg group, 260-272 subjects). Note that subjects who received placebo at Weeks 0 and 4 were included.

alkaline phosphatase were selected as statistically significant ($P < 0.005$) covariates on CL/F and body weight, race, and diabetes co-morbidity were selected as statistically significant covariates on Vd/F. Of these covariates, the inter-subject variability due to body weight, diabetes co-morbidity, or positive immune response to ustekinumab was ≥20%.

The final model-predicted CL/F and Vd/F values (0.68 L/day and 19.5 L, respectively [median]) were approximately 55% and 37% higher, respectively, in subjects weighing >100 kg compared to subjects weighing ≤100 kg (0.44 L/day and 14.2 L, respectively [median]) and the estimated steady-state trough serum concentration of ustekinumab was approximately 30% lower in subjects weighing >100 kg compared to subjects weighing ≤100 kg.

The final model-predicted CL/F and Vd/F values were approximately 28.7% and 13.2% higher, respectively, in subjects with diabetes co-morbidity compared to subjects without diabetes and the estimated trough serum ustekinumab concentration and the estimated $AUC_\infty$ value were approximately 20% lower in subjects with diabetes compared to those without diabetes. Moreover, the trough serum ustekinumab concentration and $AUC_\infty$ value were approximately 40% to 50% lower in subjects with diabetes weighing >100 kg compared to those without diabetes weighing ≤100 kg.

Although the incidence of anti-ustekinumab antibody positive subjects was as low as approximately 5%, the final model-predicted CL/F value was 35.5% higher in subjects positive for anti-ustekinumab antibodies compared to antibody-negative subjects (including inconclusive subjects).

The final model-predicted CL/F value was 5.9% higher in women compared to men and the Vd/F value was 11.1% higher in non-white subjects compared to white subjects. It was considered that the effects of the renal function (creatinine clearance) and hepatic function (albumin and alkaline phosphatase) on the pharmacokinetics of ustekinumab are also small, though assessed in a limited fashion. The potential impact of 28 concomitant medications most frequently used by subjects on the CL/F of ustekinumab were evaluated in the PPK analysis and none of the concomitant medications had a significant effect.

**4.(i).A.(3) Comparison of pharmacokinetics of ustekinumab between Japanese and foreign patients (5.3.3.3.1, 5.3.3.5.2)**

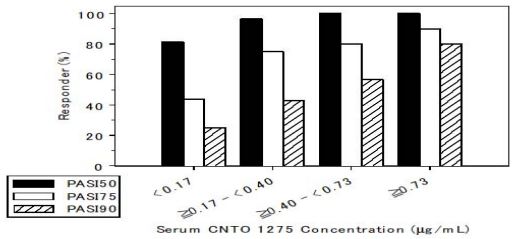
Using the data from Japanese Study JPN-01 and Foreign Study T04, the pharmacokinetics of a single subcutaneous dose of ustekinumab were compared. The median $C_{max}$ and $AUC_\infty$ were 1.07- to 1.81-fold higher in Japanese patients with psoriasis compared to foreign patients and as body weight of foreign patients with psoriasis (median body weight, 89.0 kg) was 1.34-fold heavier than body weight of Japanese patients with psoriasis (median body weight, 66.20 kg), it was discussed that the pharmacokinetic differences between Japanese and foreign patients were potentially due to the effect of body weight. Using the data from Japanese Study JPN-02 and Foreign Studies T08 and T09, the pharmacokinetics of multiple subcutaneous doses of ustekinumab were also compared. The trough

serum concentrations of ustekinumab (median) at Week 28 were 0.25 μg/mL in the 45 mg group and 0.65 μg/mL in the 90 mg group in Japanese patients, which were 0.96- to 1.19-fold and 1.33- to 1.38-fold higher, respectively, than those in foreign patients (0.21-0.26 and 0.47-0.49 μg/mL, respectively). Based on comparison of serum ustekinumab concentrations among subjects stratified by body weight (≤70 kg or >70 kg; ≤100 kg or >100 kg), it was discussed that these differences were also due to differences in body weight.

Furthermore, as covariates in the final model obtained from the PPK analysis of phase III studies in foreign patients with psoriasis (Studies T08 and T09), the subject background data from Japanese Study JPN-02 were used to predict the serum ustekinumab concentration over time in Japanese patients with psoriasis. As a result, although the observed concentrations at Weeks 2 and 20 fell outside of the 5-to-95 percentile range of the predicted values, it was explained that the pharmacokinetic differences between Japanese and foreign patients were due to the confounding effect of body weight, as the predicted values almost agreed with the observed values.

**4.(i).A.(4) Correlation between serum ustekinumab concentration and efficacy in psoriasis patients (5.3.5.1.2-1, 5.3.5.3.1)**

In Japanese Study JPN-02, the proportions of subjects who achieved Psoriasis Area and Severity Index[9] (PASI) 50, 75, and 90 responses (PASI 50, PASI 75, and PASI 90 response rates, respectively) at Week 28 by serum ustekinumab (trough) concentrations following multiple subcutaneous administrations of 45 mg or 90 mg of ustekinumab were as shown in Figure 1. The PASI 75 and PASI 90 response rates increased with increasing serum ustekinumab concentrations. Foreign Studies T08 and T09 also showed a similar trend. According to subgroup analyses of responders, partial responders and nonresponders (subjects who achieved a ≥75%, ≥50% and <75%, and <50% improvement in PASI score from baseline, respectively) at Week 28 in each of Studies JPN-02, T08, and T09, the serum ustekinumab (trough) concentration (median) was higher in this order.




| Serum ustekinumab concentration (μg/mL) | <0.17 | ≥0.17 - <0.40 | ≥0.40 - <0.73 | ≥0.73 |
|---|---|---|---|---|
| n | 32 | 28 | 30 | 30 |

Figure 1. PASI 50, 75, and 90 response rates by serum ustekinumab concentrations; Week 28 (Study JPN-02)

## *4.(i).B Outline of the review by PMDA*

**4.(i).B.(1) Racial differences in pharmacokinetic (PK)/pharmacodynamic (PD) profile**

It was explained that higher serum ustekinumab concentrations in Japanese patients compared to foreign patients were due to lower body weight of Japanese patients compared to foreign patients.

[9] The body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for erythema, infiltration/induration, and scaling, which are each rated on a 5-point scale and for area of involvement. For each of the four body areas, the three symptom scores are added and then multiplied by the area score. Each body region's score is then multiplied by the proportions to reflect its contribution to total body area (10% for head, 20% for upper extremities, 30% for trunk, 40% for lower extremities). The scores for all four body areas are added to yield the overall PASI score (Scores range from 0 to 72.0).

Meanwhile, the trough concentration was higher, but the PASI 75 response rate tended to be lower in Japanese patients compared to foreign patients. PMDA asked the applicant to discuss racial differences in the pharmacokinetic (PK)/pharmacodynamic (PD) profile of ustekinumab.

The applicant explained as follows:
Since BSA involvement and PASI score at baseline were higher in Japanese patients with psoriasis (Study JPN-02) compared to foreign patients with psoriasis (Studies T08 and T09), the applicant considered that the severity of psoriasis at baseline may affect the pharmacokinetics and efficacy of ustekinumab. Thus, baseline PASI, Physician's Global Assessment (PGA), and Dermatology Life Quality Index scores related to severity and disease duration (years) were evaluated as potential covariates in the PPK and PPK/PD analyses of the data from Studies T08 and T09. As a result, none of them were statistically significant covariates. Also when the effects of the severity of psoriasis at baseline and disease duration (years) on the PASI response rate were evaluated by subgroup analyses of Studies JPN-02 and T08 and T09, there was no clear correlation between these factors and efficacy and moreover, no effects of other patient background factors on efficacy were suggested.

PMDA concluded that although the cause for differences in the PK/PD profile between Japanese and foreign patients is not clear, ustekinumab is generally highly effective in treating skin symptoms and these differences are not clinically relevant.

**4.(i).B.(2) Pharmacokinetics and clinical response in patients with diabetes co-morbidity**
Foreign Studies T08 and T09 showed a trend toward lower trough concentrations and reduced efficacy in patients with diabetes compared to those without diabetes and body weight and diabetes co-morbidity were selected as covariates on CL/F and Vd/F in the PPK analysis. PMDA asked the applicant to discuss its cause and explain whether dose adjustment is required for patients with diabetes co-morbidity.

The applicant explained as follows:
The trough serum concentration of ustekinumab estimated from the final model obtained in the PPK analysis of Studies T08 and T09 was approximately 20% lower in subjects with diabetes compared to subjects without diabetes of the same body weight and according to the pooled data from Studies T08 and T09, the PASI 75 response rate was slightly lower in subjects with diabetes than in subjects without diabetes in both subgroups of subjects weighing ≤100 kg or >100 kg. Thus, it is considered that lower serum ustekinumab concentrations and reduced efficacy in patients with diabetes are due to the effects of not only body weight but also diabetes itself, which may be attributable to altered vascular permeability and lymph distribution of drugs in patients with diabetes. On the other hand, in order to determine the effect of the severity of diabetes, the relationship between baseline HbA1c and trough serum concentration of ustekinumab/percent improvement in PASI score in Studies T08 and T09 was examined. As a result, there was a statistically significant but weak negative correlation between baseline HbA1c and both trough serum concentration of ustekinumab and percent

improvement in PASI score. Thus, no specific dose adjustment is required for patients with diabetes co-morbidity.

PMDA accepts the above response at present, but considers that as the number of subjects with high HbA1c was limited in the clinical studies, the efficacy of ustekinumab in patients with diabetes co-morbidity needs to be further investigated, including the effect of the severity of diabetes, via post-marketing surveillance.

**4.(i).B.(3) Anti-ustekinumab antibodies**

The applicant explained the incidence of anti-ustekinumab antibody production and its relationship with the pharmacokinetics and efficacy of ustekinumab, etc. as follows:

The incidences of anti-ustekinumab antibody positive subjects in Japanese Study JPN-02 and Foreign Studies T04, T08, and T09 were 6.5% (10 of 153 subjects) [through Week 72], 4.1% (12 of 293 subjects) [through Week 52], 5.1% (38 of 746 subjects) [through Week 76], and 5.3% (64 of 1202 subjects) [through Week 88], respectively, and no differences between Japanese and foreign patients with psoriasis were observed. Japanese Study JPN-02 showed that the incidence of anti-ustekinumab antibody positive subjects tended to be higher in the 45 mg group (9.4%, 6 of 64 subjects) than in the 90 mg group (3.3%, 2 of 61 subjects) and a similar trend was observed also in foreign patients with psoriasis. When stratified by body weight, the incidence of anti-ustekinumab antibody positive subjects was lower in subjects weighing ≤100 kg (3.6%, 48 of 1341 subjects) than in subjects weighing >100 kg (9.1%, 55 of 606 subjects) in Studies T08 and T09. Anti-ustekinumab antibodies were detected by around Week 28 in Study JPN-02 and by around Week 52 in Studies T08 and T09 and 4.4% (13 of 297 subjects) of subjects who were retreated with ustekinumab after withdrawal from ustekinumab therapy developed anti-ustekinumab antibodies, which was similar to the incidence in the overall study population.

In Studies T02, T04, and T08, samples from 50 of 51 subjects positive for anti-ustekinumab antibodies were assessed for ustekinumab neutralizing potential and 29 (58.0%) of the 50 subjects were positive for neutralizing antibodies that are able to neutralize the pharmacological activity of ustekinumab. Some of the anti-ustekinumab antibody positive subjects were not positive for neutralizing antibodies. They had low antibody titers and probably, the neutralizing effect of antibodies could not be detected.

Following multiple subcutaneous administrations of ustekinumab to Japanese and foreign patients with psoriasis, anti-ustekinumab antibody positive subjects tended to have lower serum ustekinumab concentrations (median) than antibody negative subjects.

The PASI 75 and PASI 90 response rates at Week 28 tended to be lower in anti-ustekinumab antibody positive subjects compared to antibody negative subjects in Japanese Study JPN-02 and a similar trend was observed also in foreign studies. However, since many antibody-positive subjects achieved a

PASI 50 response and some achieved a PASI 75 response, it was discussed that anti-ustekinumab antibody development has no significant impact on clinical response.

PMDA considers as follows:
Based on the above, no clinically relevant problems with anti-ustekinumab antibody development have been suggested at present. Meanwhile, the relationship between neutralizing activity of antibodies and the efficacy and pharmacokinetics of ustekinumab has not adequately been examined and the proportion of antibody positive subjects who were positive for neutralizing antibodies tended to be relatively high (≥50%). Taking account of these points, a further investigation on antibodies and their neutralizing activity etc. in patients with markedly reduced efficacy during continued treatment is necessary.

**4.(ii) Summary of clinical efficacy and safety**

***4.(ii).A Summary of the submitted data***

As the efficacy and safety evaluation data, the results from a phase I study (Study JNS009-JPN-01 [5.3.3.2.1]) and a phase II/III study (Study JNS009-JPN-02 [5.3.5.1.2-1 to 5.3.5.1.2-2]) in Japanese patients with psoriasis and a phase I single intravenous administration study (Study C0379T01 [5.3.3.2.2]), a phase I single subcutaneous administration study (Study C0379T02 [5.3.3.2.3]), a phase II study (Study C0379T04 [5.3.5.1.1]), a phase II study (Study C0743T10 [5.3.5.4.1]), a phase III study (Study C0743T08 [5.3.5.1.3-1 to 5.3.5.1.3-3]), and a phase III study (Study C0743T09 [5.3.5.1.4-1 to 5.3.5.1.4-3]) in foreign patients with psoriasis were submitted.

**4.(ii).A.(1) Studies in Japanese patients**

**4.(ii).A.(1).1) Phase I study (5.3.3.2.1, JNS009-JPN-01 [February 2006 to March 2007])**

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in patients with psoriasis vulgaris (Target sample size of 24 subjects [6 subjects each in the ustekinumab 22.5 mg, 45 mg, and 90 mg and placebo groups]) to evaluate the efficacy, safety, and pharmacokinetics of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

A single subcutaneous dose of 22.5 mg of ustekinumab (6 subjects) or placebo (2 subjects) was to be administered in STEP1, a single subcutaneous dose of 45 mg of ustekinumab (6 subjects) or placebo (2 subjects) in STEP2, and a single subcutaneous dose of 90 mg of ustekinumab (6 subjects) or placebo (2 subjects) in STEP3. After safety was confirmed in each STEP, the study was to move to the next STEP. Subjects were followed through Week 24.

All of the 24 subjects treated were included in the Full Analysis Set (FAS), which was used as the safety population, and 23 subjects (6 subjects in the 22.5 mg group, 6 subjects in the 45 mg group, 6 subjects in the 90 mg group, 5 subjects in the placebo group), excluding 1 subject in the placebo group

who received rescue medication due to exacerbation of the primary disease, were included in the Per Protocol Set, which was used as the primary efficacy population.

The Psoriasis Area and Severity Index[10] (PASI) 75 response rate[11] at Week 12 was an efficacy endpoint. The PASI 75 response rates at Week 12 were 33.3% (2 of 6 subjects) in the 22.5 mg group, 100% (6 of 6 subjects) in the 45 mg group, 75% (3 of 4 subjects) in the 90 mg group, and 0% in the placebo group, and the ustekinumab groups showed greater improvement compared to the placebo group.

Adverse events (including abnormal laboratory test values) occurred in all subjects (24 of 24 subjects). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Adverse drug reactions[12] occurred in all subjects (24 of 24 subjects) and those reported by ≥2 subjects in any of the ustekinumab groups were nasopharyngitis [33.3% (2 of 6 subjects) in the 22.5 mg group, 16.7% (1 of 6 subjects) in the 45 mg group, 33.3% (2 of 6 subjects) in the 90 mg group, 0% (0 of 6 subjects) in the placebo group], activated partial thromboplastin time prolonged [50.0% (3 of 6 subjects) in the 22.5 mg group, 33.3% (2 of 6 subjects) in the 45 mg group, 33.3% (2 of 6 subjects) in the 90 mg group, 0% (0 of 6 subjects) in the placebo group], and B-lymphocyte count decreased [33.3% (2 of 6 subjects) in the 22.5 mg group, 50.0% (3 of 6 subjects) in the 45 mg group, 16.7% (1 of 6 subjects) in the 90 mg group, 66.7% (4 of 6 subjects) in the placebo group].

**4.(ii).A.(1).2) Phase II/III study (5.3.5.1.2-1 to 5.3.5.1.2-2, JNS009-JPN-02 [March 2008 to March 2010])**

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in Japanese patients with moderate to severe[13] plaque psoriasis (psoriasis vulgaris, psoriatic arthritis) (Target sample size of 150 [60 subjects per active treatment group, 30 subjects in the placebo group]) to evaluate the efficacy and safety of ustekinumab.

Ustekinumab 45 or 90 mg or placebo was to be subcutaneously administered according to Table 12. Subjects were followed for efficacy and safety through Week 64 and Week 72, respectively.

When the pharmacokinetics of ustekinumab were compared between Japanese Study JPN-01 and Foreign Study T04, the pharmacokinetics of ustekinumab were considered similar between Japanese

[10] The body is divided into 4 regions: the head, upper extremities, trunk, and lower extremities. Each of these areas is assessed separately for erythema, infiltration/induration, and scaling, which are each rated on a 5-point scale and for area of involvement. For each of the four body areas, the three symptom scores are added and then multiplied by the area score. Each body region's score is then multiplied by the proportions to reflect its contribution to total body area (10% for head, 20% for upper extremities, 30% for trunk, 40% for lower extremities). The scores for all four body areas are added to yield the overall PASI score (Scores range from 0 to 72.0).

[11] The proportion of subjects who achieved a ≥75% reduction in PASI score from baseline.

[12] Adverse events for which a causal relationship to study drug could not be denied (adverse events other than those assessed as "unrelated to" study drug).

[13] Body surface area (BSA) involvement of ≥10% and PASI score of ≥12.

and foreign patients of the same body weight range [see "4.(i) Summary of clinical pharmacology studies"] and 9 of 10 patients who received 45 or 90 mg of ustekinumab achieved a PASI 75 response in Study JPN-01. Thus, for this study, the same dosing regimen as that for foreign phase III studies (Studies T08 and T09) was selected.

Table 12. Ustekinumab dosing schedule for each treatment group

| | Week 0 | Week 4 | Week 12 | Week 16 | Every 12 weeks after Week 28 through Week 52 |
|---|---|---|---|---|---|
| 45 mg group | 45 mg | 45 mg | Placebo | 45 mg | 45 mg |
| 90 mg group | 90 mg | 90 mg | Placebo | 90 mg | 90 mg |
| Placebo→45 mg group | Placebo | Placebo | 45 mg | 45 mg | 45 mg |
| Placebo→90 mg group | Placebo | Placebo | 90 mg | 90 mg | 90 mg |

All of the 158 subjects treated (64 subjects in the 45 mg group, 62 subjects in the 90 mg group, 32 subjects in the placebo group) were included in the safety population and 157 subjects (64 subjects in the 45 mg group, 62 subjects in the 90 mg group, 15 subjects in the placebo→45 mg group, 16 subjects in the placebo→90 mg group), excluding 1 subject for whom an emergency code break was required before efficacy data collection, were included in the FAS, which was used as the primary efficacy population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 was 59.4% (38 of 64 subjects) in the 45 mg group, 67.7% (42 of 62 subjects) in the 90 mg group, and 6.5% (2 of 31 subjects) in the placebo group, as shown in Table 13, and the differences between both of the ustekinumab groups and the placebo group were statistically significant ($P < 0.0001$ for both [Fisher's exact test], using Holm's method). The secondary endpoints of the PASI 50 response rate and the PASI 90 response rate were as shown in Table 13.

Table 13. PASI response rate at Week 12

| | Placebo | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|---|
| PASI 50 response rate | 12.9 (4/31) | 82.8 (53/64) | 83.9 (52/62) |
| PASI 75 response rate | 6.5 (2/31) | 59.4 (38/64) | 67.7 (42/62) |
| PASI 90 response rate | 3.2 (1/31) | 32.8 (21/64) | 43.5 (27/62) |

% (n)

Of the 157 patients, 22 patients had joint symptoms and among these patients, the PASI 75 response rates at Week 12 were 83.3% (5 of 6 subjects) in the 45 mg group, 46.2% (6 of 13 subjects) in the 90 mg group, and 0% (0 of 3 subjects) in the placebo group.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 65.6% (42 of 64 subjects) (85 events) in the 45 mg group, 59.7% (37 of 62 subjects) (80 events) in the 90 mg group, and 65.6% (21 of 32 subjects) (38 events) in the placebo group. No deaths were reported. The incidences of serious adverse events were 4.8% (3 of 62 subjects) (4 events) (pneumonia; prostate cancer; and psoriasis and osteonecrosis, 1 subject each) in the 90 mg group and 6.3% (2 of 32 subjects) (3 events) (cardiac failure congestive [1 subject], psoriasis and dermatitis exfoliative [1 subject]) in the placebo group, and although a causal relationship to study drug could not

be denied for pneumonia, prostate cancer, and psoriasis in the 90 mg group and cardiac failure congestive in the placebo group, the outcomes of all events were reported as resolved or improved. The incidences of adverse events leading to treatment discontinuation were 6.5% (4 of 62 subjects) (4 events) (psoriasis [2 subjects], pneumonia [1 subject], prostate cancer [1 subject]) in the 90 mg group and 6.3% (2 of 32 subjects) (3 events) (psoriasis [1 subject], psoriasis and dermatitis exfoliative [1 subject]) in the placebo group, and a causal relationship to study drug could not be denied for pneumonia, prostate cancer, and psoriasis (2 subjects) in the 90 mg group and the outcomes of all events were reported as resolved or improved.

The incidences of adverse drug reactions were 54.7% (35 of 64 subjects) (59 events) in the 45 mg group, 45.2% (28 of 62 subjects) (53 events) in the 90 mg group, and 59.4% (19 of 32 subjects) (30 events) in the placebo group and those reported by ≥2 subjects in any group were as shown in Table 14.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 72[14] were 96.9% (62 of 64 subjects) (447 events) in the 45 mg group, 98.4% (61 of 62 subjects) (417 events) in the 90 mg group, 93.3% (14 of 15 subjects) (89 events) in the placebo→45 mg group, and 100% (13 of 13 subjects) (69 events) in the placebo→90 mg group. No deaths were reported. The incidences of serious adverse events were 7.8% (5 of 64 subjects) (7 events) in the 45 mg group, 9.7% (6 of 62 subjects) (9 events) in the 90 mg group, 6.7% (1 of 15 subjects) (1 event) in the placebo→45 mg group, and 7.7% (1 of 13 subjects) (1 event) in the placebo→90 mg group. Those occurring after Week 12 were as follows: 45 mg group (fall; cellulitis; cervix carcinoma stage 0; cataract; and pharyngitis, colonic polyp, and diabetes mellitus, 1 subject each), 90 mg group (dislocation of the prosthetic femoral head; fall; cerebral haemorrhage; and cataract, 1 subject each), placebo→45 mg group (lumbar spinal stenosis [1 subject]), and placebo→90 mg group (electrocardiogram abnormal [1 subject]). Although a causal relationship to study drug could not be denied for pharyngitis, colonic polyp, and cellulitis in the 45 mg group, cerebral haemorrhage and cataract in the 90 mg group, and lumbar spinal stenosis in the placebo→45 mg group, the outcomes of all events were reported as resolved or improved, except that the outcome of cerebral haemorrhage (1 subject in the 90 mg group) was reported as improved with sequelae.

The incidences of adverse events leading to treatment discontinuation after Week 12 were 1.6% (1 of 64 subjects) (1 event) (cervix carcinoma stage 0) in the 45 mg group, 1.6% (1 of 62 subjects) (1 event) (cerebral haemorrhage) in the 90 mg group, and 7.7% (1 of 13 subjects) (1 event) (hepatic steatosis) in the placebo→90 mg group. Although the 1 subject discontinued treatment due to hepatic steatosis after Week 12, hepatic steatosis occurred during the placebo administration period before Week 12.

[14] From Week 12 through Week 72, after crossover to ustekinumab.

The incidences of adverse drug reactions were 87.5% (56 of 64 subjects) (304 events) in the 45 mg group, 87.1% (54 of 62 subjects) (300 events) in the 90 mg group, 93.3% (14 of 15 subjects) (74 events) in the placebo→45 mg group, and 92.3% (12 of 13 subjects) (42 events) in the placebo→90 mg group. Adverse drug reactions reported by ≥2 subjects in any group were as shown in Table 15.

Table 14. Adverse drug reactions reported by ≥2 subjects in any group (through Week 12)

| Preferred terms | Placebo | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|---|
| Nasopharyngitis | 2 (6.3) | 9 (14.1) | 8 (12.9) |
| Folliculitis | 0 | 1 (1.6) | 2 (3.2) |
| Psoriasis | 5 (15.6) | 1 (1.6) | 3 (4.8) |
| Eczema | 0 | 1 (1.6) | 2 (3.2) |
| Arthralgia | 0 | 3 (4.7) | 0 |
| Blood triglycerides increased | 1 (3.1) | 4 (6.3) | 0 |
| Eosinophil count increased | 1 (3.1) | 2 (3.1) | 3 (4.8) |
| Basophil count increased | 0 | 2 (3.1) | 2 (3.2) |
| Blood uric acid increased | 0 | 1 (1.6) | 2 (3.2) |
| Lymphocyte count decreased | 0 | 2 (3.1) | 0 |

n (%)

Table 15. Adverse drug reactions reported by ≥2 subjects in any group (through Week 72)

| Preferred terms | Placebo→45 mg | Placebo→90 mg | 45 mg | 90 mg |
|---|---|---|---|---|
| Nasopharyngitis | 7 (46.7) | 7 (53.8) | 27 (42.2) | 26 (41.9) |
| Influenza | 0 | 0 | 2 (3.1) | 5 (8.1) |
| Folliculitis | 2 (13.3) | 0 | 2 (3.1) | 4 (6.5) |
| Cystitis | 0 | 0 | 2 (3.1) | 0 |
| Skin papilloma | 0 | 0 | 0 | 3 (4.8) |
| Seasonal allergy | 1 (6.7) | 0 | 2 (3.1) | 5 (8.1) |
| Hyperlipidaemia | 1 (6.7) | 0 | 3 (4.7) | 0 |
| Headache | 0 | 1 (7.7) | 5 (7.8) | 1 (1.6) |
| Conjunctivitis | 0 | 0 | 2 (3.1) | 1 (1.6) |
| Ventricular extrasystoles | 0 | 0 | 2 (3.1) | 2 (3.2) |
| Hypertension | 0 | 0 | 2 (3.1) | 4 (6.5) |
| Rhinitis allergic | 1 (6.7) | 0 | 1 (1.6) | 4 (6.5) |
| Oropharyngeal pain | 0 | 1 (7.7) | 0 | 2 (3.2) |
| Dental caries | 0 | 0 | 3 (4.7) | 3 (4.8) |
| Diarrhoea | 0 | 1 (7.7) | 4 (6.3) | 0 |
| Periodontal disease | 1 (6.7) | 0 | 0 | 2 (3.2) |
| Enterocolitis | 0 | 0 | 2 (3.1) | 0 |
| Hepatic function abnormal | 0 | 0 | 3 (4.7) | 3 (4.8) |
| Eczema | 1 (6.7) | 0 | 2 (3.1) | 3 (4.8) |
| Psoriasis | 0 | 0 | 3 (4.7) | 4 (6.5) |
| Urticaria | 1 (6.7) | 1 (7.7) | 1 (1.6) | 2 (3.2) |
| Acne | 0 | 1 (7.7) | 0 | 3 (4.8) |
| Xeroderma | 1 (6.7) | 0 | 2 (3.1) | 2 (3.2) |
| Heat rash | 0 | 0 | 2 (3.1) | 0 |
| Pruritus | 0 | 0 | 2 (3.1) | 0 |
| Back pain | 1 (6.7) | 0 | 1 (1.6) | 2 (3.2) |
| Arthralgia | 0 | 1 (7.7) | 6 (9.4) | 1 (1.6) |
| Pain in extremity | 0 | 0 | 2 (3.1) | 0 |
| Pyrexia | 1 (6.7) | 1 (7.7) | 2 (3.1) | 0 |
| Blood triglycerides increased | 2 (13.3) | 1 (7.7) | 10 (15.6) | 8 (12.9) |
| Blood creatine phosphokinase increased | 2 (13.3) | 2 (15.4) | 7 (10.9) | 9 (14.5) |
| Alanine aminotransferase increased | 2 (13.3) | 2 (15.4) | 4 (6.3) | 6 (9.7) |
| Eosinophil count increased | 0 | 0 | 4 (6.3) | 6 (9.7) |
| White blood cell count increased | 0 | 1 (7.7) | 4 (6.3) | 4 (6.5) |
| Blood lactate dehydrogenase increased | 1 (6.7) | 0 | 5 (7.8) | 3 (4.8) |
| Lymphocyte count decreased | 1 (6.7) | 0 | 5 (7.8) | 1 (1.6) |
| Basophil count increased | 0 | 0 | 3 (4.7) | 4 (6.5) |
| Glucose urine present | 1 (6.7) | 0 | 2 (3.1) | 3 (4.8) |
| Blood cholesterol increased | 1 (6.7) | 0 | 3 (4.7) | 0 |
| Blood amylase increased | 0 | 1 (7.7) | 1 (1.6) | 2 (3.2) |
| Blood bilirubin increased | 0 | 1 (7.7) | 2 (3.1) | 1 (1.6) |
| C-reactive protein increased | 1 (6.7) | 0 | 1 (1.6) | 3 (4.8) |

| | | | | |
|---|---|---|---|---|
| Protein urine present | 0 | 0 | 0 | 3 (4.8) |
| Blood creatinine increased | 0 | 0 | 0 | 2 (3.2) |
| Blood uric acid increased | 0 | 0 | 1 (1.6) | 2 (3.2) |
| Liver function test abnormal | 0 | 0 | 0 | 3 (4.8) |
| Red blood cell count increased | 1 (6.7) | 0 | 0 | 2 (3.2) |
| White blood cell count decreased | 0 | 0 | 2 (3.1) | 1 (1.6) |
| Blood phosphorus decreased | 1 (6.7) | 0 | 0 | 2 (3.2) |
| Blood phosphorus increased | 0 | 0 | 2 (3.1) | 0 |
| Blood urea increased | 0 | 0 | 0 | 2 (3.2) |
| Blood urine present | 0 | 0 | 0 | 2 (3.2) |
| Weight increased | 0 | 0 | 2 (3.1) | 0 |

n(%)

Based on the above, the applicant explained as follows:

The efficacy of ustekinumab was confirmed. When the efficacy of ustekinumab at different dose levels was examined, the PASI 75 response rate at Week 12 was 8.3% higher in the 90 mg group compared to the 45 mg group while the PASI 50 response rate was almost the same in the 45 mg and 90 mg groups, which indicated that both dose levels of ustekinumab can achieve clinically significant improvement in skin lesions in most patients, etc. Thus, the recommended clinical dose of ustekinumab should be 45 mg. On the other hand, given that foreign studies showed that the trough serum concentration of ustekinumab and the PASI 75 response rate in the 90 mg group tended to be lower in subjects weighing >100 kg compared to those weighing ≤100 kg, etc., it was decided that a 90 mg dose may be used in patients weighing >100 kg.

**4.(ii).A.(2) Studies in foreign patients**

**4.(ii).A.(2).1) Single intravenous administration study (5.3.3.2.2, C0379T01 [April 2001 to August 2002])**

An open-label, uncontrolled study was conducted in patients with moderate to severe psoriasis vulgaris (Target sample size of 23 [4 subjects each in the 0.09 and 0.27 mg/kg groups, 5 subjects each in the 0.9, 4.5, and 18 mg/kg groups]) to evaluate the pharmacokinetics, efficacy, and safety of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

A single dose of 0.09, 0.27, 0.90, 4.5, or 18 mg/kg[15] of ustekinumab was to be administered as an intravenous infusion over ≥2 hours. Ustekinumab treatment was started with the lowest dose and after safety was confirmed, the dose was to be escalated to the next dose level. Subjects were followed through Week 16.

All of the 18 subjects treated[16] (4 subjects each in the 0.09 and 0.27 mg/kg groups, 5 subjects each in the 0.9 and 4.5 mg/kg groups) were included in the safety and efficacy populations.

The percent improvement in PASI score from baseline (mean ± SD) was an efficacy endpoint. The percent improvements in the 0.09, 0.27, 0.9, and 4.5 mg/kg groups were 68.5 ± 25.1%, 54.3 ± 49.1%,

[15] Although the study was intended to be conducted at doses of 0.1, 0.3, 1.0, 5.0, and 20 mg/kg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

[16] An 18 mg/kg group was not included in the study due to protocol amendments.

73.6 ± 20.0%, and 97.1 ± 4.9%, respectively, at Week 12, and 58.1 ± 32.5%, 50.0 ± 45.0%, 80.4 ± 18.9%, and 94.9 ± 7.2%, respectively, at Week 16.

Adverse events (including abnormal laboratory test values) occurred in all subjects (18 of 18 subjects). No deaths were reported. A serious adverse event occurred in 1 subject in the 4.5 mg/kg group (herniated disk) and its causal relationship to study drug was denied. There were no adverse events leading to treatment discontinuation.

Adverse drug reactions occurred in all subjects except for 2 subjects in the 0.9 mg/kg group and 1 subject in the 4.5 mg/kg group. Those reported by ≥2 subjects in any group were lymphocyte count decreased (3 subjects in the 0.09 mg/kg group, 3 subjects in the 0.27 mg/kg group, 2 subjects in the 0.9 mg/kg group, 2 subjects in the 4.5 mg/kg group) and headache (1 subject in the 0.09 mg/kg group, 3 subjects in the 0.27 mg/kg group, 1 subject in the 0.9 mg/kg group, 1 subject in the 4.5 mg/kg group).

**4.(ii).A.(2).2) Single subcutaneous administration study (5.3.3.2.3, C0379T02 [June 2002 to May 2003])**

A placebo-controlled, double-blind, parallel-group, comparative study was conducted in patients with moderate to severe psoriasis vulgaris (Target sample size of 20 [4 subjects each in the ustekinumab 0.27, 0.675, 1.35, and 2.7 mg/kg and placebo groups]) to evaluate the pharmacokinetics, efficacy, and safety of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

In Cohort 1, a single subcutaneous dose of 0.27 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 2, a single subcutaneous dose of 0.675 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 3, a single subcutaneous dose of 1.35 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 4, a single subcutaneous dose of 2.7 mg/kg of ustekinumab (4 subjects) or placebo (1 subject)[17] was to be administered. After safety was confirmed in each cohort, the next dose cohort was to be initiated. Subjects were followed through Week 24.

All of the 21 subjects treated (5 subjects in the 0.27 mg/kg group, 4 subjects each in the 0.675, 1.35, and 2.7 mg/kg and placebo groups) were included in the safety and efficacy populations.

The percent improvement in PASI score from baseline (mean ± SD) was an efficacy endpoint. The percent improvements in the 0.27, 0.675, 1.35, 2.7 mg/kg, and placebo groups were 53.1 ± 26.0%, 76.7 ± 13.3%, 57.3 ± 11.3%, 85.4 ± 8.0%, and 43.4 ± 27.4%, respectively, at Week 12 and 25.1 ± 32.8%, 33.2 ± 45.1%, 44.9 ± 27.5%, 76.5 ± 10.2%, and -5.0 ± 52.6%, respectively, at Week 24.

[17] Although the study was intended to be conducted at doses of 0.3, 0.75, 1.5, and 3.0 mg/kg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

The incidences of adverse events (including abnormal laboratory test values) were 100% (5 of 5 subjects) in the 0.27 mg/kg group, 75% (3 of 4 subjects) in the 0.675 mg/kg group, 75% (3 of 4 subjects) in the 1.35 mg/kg group, 100% (4 of 4 subjects) in the 2.7 mg/kg group, and 100% (4 of 4 subjects) in the placebo group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

The incidences of adverse drug reactions were 100% (5 of 5 subjects) in the 0.27 mg/kg group, 75% (3 of 4 subjects) in the 0.675 mg/kg group, 50% (2 of 4 subjects) in the 1.35 mg/kg group, 100% (4 of 4 subjects) in the 2.7 mg/kg group, and 75% (3 of 4 subjects) in the placebo group, and those reported by ≥2 subjects in any group were blood creatine phosphokinase increased (3 subjects in the 0.27 mg group, 1 subject in the 0.675 mg/kg group, 0 subjects in the 1.35 mg/kg group, 1 subject in the 2.7 mg/kg group, 1 subject in the placebo group).

**4.(ii).A.(2).3) Phase II study (5.3.5.1.1, C0379T04 [June 2003 to March 2005])**

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 300 [60 subjects per group]) to evaluate the efficacy and safety of ustekinumab.

According to Table 16, 45 or 90 mg[18] of ustekinumab or placebo was to be administered subcutaneously. Subjects were followed for safety and efficacy through Week 32 and Week 36, respectively.

In Study T01, 2 of 4 subjects in the 0.27 mg/kg group achieved a PASI 75 response and the bioavailability of ustekinumab following subcutaneous administration was approximately 62.5% and the mean body weight of psoriasis patients was approximately 95 kg. Taking account of these findings, an ustekinumab subcutaneous fixed dose of 45 mg was selected as the lowest dose for this study. Since subjects with $AUC_{\infty}$ >450 μg·day/mL or $C_{max}$ >27 μg/mL achieved a PASI 75 response in Studies T01 and T02, a compartment model analysis was performed using the data from the two studies and 90 mg (single dose), 180 mg (45 mg/week × 4), and 360 mg (90 mg/week × 4) as well as 45 mg (single dose) were selected to span the above-mentioned levels of $AUC_{\infty}$ and $C_{max}$.

Table 16. Ustekinumab dosing schedule for each treatment group

| | Week 0 | Weeks 1, 2, 3 | Week 16 | Week 20 |
|---|---|---|---|---|
| 45 mg single-dose group | Ustekinumab 45 mg | Placebo | Ustekinumab 45 mg or placebo[a] | Placebo |
| 90 mg single-dose group | Ustekinumab 90 mg | Placebo | Ustekinumab 90 mg or placebo[a] | Placebo |
| 45 mg multiple-dose group | Ustekinumab 45 mg | Ustekinumab 45 mg | Ustekinumab 45 mg or placebo[a] | Placebo |
| 90 mg multiple-dose group | Ustekinumab 90 mg | Ustekinumab 90 mg | Ustekinumab 90 mg or placebo[a] | Placebo |
| Placebo group | Placebo | Placebo | Placebo | Ustekinumab 90 mg |

a: Subjects with relative PGA ≥3 were to receive ustekinumab and subjects with relative PGA <3 were to receive placebo.

[18] Although the study was intended to be conducted at doses of 50 and 100 mg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

The efficacy population included 320 randomized subjects (64 subjects per group). Excluding 2 subjects who did not receive study drug (1 subject each in the 45 mg single-dose and 90 mg single-dose groups) and including 1 subject who mistakenly received placebo before randomization, 319 subjects were included in the safety population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 was 51.6% (33 of 64 subjects) in the 45 mg single-dose group, 59.4% (38 of 64 subjects) in the 90 mg single-dose group, 67.2% (43 of 64 subjects) in the 45 mg multiple-dose group, 81.3% (52 of 64 subjects) in the 90 mg multiple-dose group, and 1.6% (1 of 64 subjects) in the placebo group and subjects treated with ustekinumab showed significantly greater improvement compared with subjects treated with placebo ($P < 0.001$, pairwise comparisons using the Chochran-Mantel-Haenzel $\chi^2$ test).

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 36 were 95.2% (60 of 63 subjects) in the 45 mg single-dose group, 87.5% (56 of 64 subjects) in the 90 mg single-dose group, 87.3% (55 of 63 subjects) in the 45 mg multiple-dose group, 72.6% (45 of 62 subjects) in the 90 mg multiple-dose group, 51.0% (25 of 49 subjects) in the placebo→90 mg (after Week 20) group, and 71.6% (48 of 67 subjects) in the placebo group (through Week 20). No deaths were reported. The incidences of serious adverse events were 4.8% (3 of 63 subjects) (acute psychosis; cellulitis; and rib fracture, 1 subject each) in the 45 mg single-dose group, 4.7% (3 of 64 subjects) (myocardial infarction; abdominal hernia; and coronary artery disease, 1 subject each) in the 90 mg single-dose group, 3.2% (2 of 63 subjects) (cerebrovascular accident; and chest pain, 1 subject each) in the 45 mg multiple-dose group, 8.1% (5 of 62 subjects) (urinary tract infection; acute myocardial infarction and viral infection; uterine leiomyoma; pneumonia and cardiac failure congestive; and acute psychosis and polysubstance dependence, 1 subject each) in the 90 mg multiple-dose group, 2.0% (1 of 49 subjects) (hepatic enzyme increased) in the placebo→90 mg (after Week 20) group, and 1.5% (1 of 67 subjects) (psoriasis) in the placebo group and a causal relationship to study drug could not be denied for cellulitis, myocardial infarction, coronary artery disease, cerebrovascular accident, urinary tract infection, acute myocardial infarction, viral infection, pneumonia, cardiac failure congestive, and hepatic enzyme increased. The outcomes of coronary artery disease, cardiac failure congestive, acute psychosis, and polysubstance dependence were reported as unresolved, but other events resolved. The incidences of adverse events leading to treatment discontinuation were 14.3% (9 of 63 subjects) in the 45 mg single-dose group, 1.6% (1 of 64 subjects) in the 90 mg single-dose group, 1.6% (1 of 63 subjects) in the 45 mg multiple-dose group, 1.6% (1 of 62 subjects) in the 90 mg multiple-dose group, and 3.0% (2 of 67 subjects) in the placebo group, and those reported by ≥2 subjects were psoriasis (2 subjects in the 45 mg single-dose group, 2 subjects in the placebo group).

The incidences of adverse drug reactions were 74.6% (47 of 63 subjects) in the 45 mg single-dose group, 68.8% (44 of 64 subjects) in the 90 mg single-dose group, 63.5% (40 of 63 subjects) in the 45 mg multiple-dose group, 48.4% (30 of 62 subjects) in the 90 mg multiple-dose group, 24.5% (12 of 49

subjects) in the placebo→90 mg (after Week 20) group, and 46.3% (31 of 67 subjects) in the placebo group (through Week 20), and those reported by ≥5% of subjects in any group were as shown in Table 17.

Table 17. Adverse drug reactions reported by ≥5% of subjects in any group

| Preferred terms | Placebo (Weeks 0-20) | Placebo→90mg (after Week 20) | 45 mg single dose | 90 mg single dose | 45 mg multiple doses | 90 mg multiple doses |
|---|---|---|---|---|---|---|
| Nasopharyngitis | 5 (7.5) | 0 | 5 (7.9) | 7 (10.9) | 3 (4.8) | 5 (8.1) |
| Upper respiratory tract infection | 4 (6.0) | 0 | 7 (11.1) | 5 (7.8) | 6 (9.5) | 3 (4.8) |
| Urinary tract infection | 0 | 0 | 3 (4.8) | 1 (1.6) | 4 (6.3) | 3 (4.8) |
| Arthralgia | 0 | 2 (4.1) | 5 (7.9) | 3 (4.7) | 0 | 3 (4.8) |
| Myalgia | 0 | 0 | 4 (6.3) | 1 (1.6) | 0 | 1 (1.6) |
| Arthritis | 4 (6.0) | 0 | 1 (1.6) | 1 (1.6) | 0 | 0 |
| Pruritus | 1 (1.5) | 0 | 7 (11.1) | 3 (4.7) | 1 (1.6) | 2 (3.2) |
| Headache | 8 (11.9) | 0 | 12 (19.0) | 9 (14.1) | 0 | 10 (16.1) |
| Diarrhoea | 0 | 0 | 2 (3.2) | 0 | 4 (6.3) | 1 (1.6) |
| Nausea | 2 (3.0) | 0 | 1 (1.6) | 3 (4.7) | 2 (3.2) | 4 (6.5) |

n (%)

**4.(ii).A.(2).4) Phase II clinical study (5.3.5.4.1, C0743T10 [December 2005 to September 2007])**

A placebo-controlled, randomized, double-blind study was conducted in patients with active psoriatic arthritis (Target sample size of 140 [70 subjects per group]) to evaluate the efficacy and safety of ustekinumab.

In Group I (ustekinumab→placebo group), 90 mg[19] of ustekinumab at Weeks 0, 1, 2, and 3 and placebo at Weeks 12 and 16 were to be administered subcutaneously. In Group II (placebo→ustekinumab group), placebo at Weeks 0, 1, 2, and 3 and 90 mg[19] of ustekinumab at Weeks 12 and 16 were to be administered subcutaneously. Subjects were followed for efficacy and safety through Week 36.

All of the 146 subjects treated (76 subjects in the ustekinumab→placebo group, 70 subjects in the placebo→ustekinumab group) were included both in the safety and primary efficacy populations.

The primary efficacy endpoint of the ACR 20 response rate at Week 12 was 42.1% (32 of 76 subjects) in the ustekinumab group, which was significantly higher than 14.3% (10 of 70 subjects) in the placebo group ($P < 0.001$).

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 60.5% (46 of 76 subjects) (107 events) in the ustekinumab group and 62.9% (44 of 70 subjects) (89 events) in the placebo group. No deaths were reported. The incidences of serious adverse events were 0% (0 of 76 subjects) (0 events) in the ustekinumab group and 4.3% (3 of 70 subjects) (3

[19] During this clinical study, it was revealed that the vials of another study drug that was not used in this study contained particulate matters. Since the lyophilized formulation of ustekinumab was also filled at the same site over the same period of time, as a precautionary measure to ensure subject's safety, the prepared solution for injection was filtered. The volume of the filtered solution for injection was approximately 0.70 mL (corresponding to 63 mg of ustekinumab). In Group I, 59 of 76 subjects received the filtered solution (63 mg of ustekinumab) for all 4 doses and 3 of the remaining 17 subjects received the filtered solution (63 mg of ustekinumab) for at least one of the 4 doses. Of 70 subjects in Group II, 57 subjects at Week 12 and 55 subjects at Week 16 received the filtered solution (63 mg of ustekinumab).

events) (myocardial infarction, gastric ulcer haemorrhage, chest pain) in the placebo group and although a causal relationship to study drug could not be denied for all events, the outcomes of all events were reported as resolved. The incidences of adverse events leading to treatment discontinuation were 1.3% (1 of 76 subjects) (1 event) (pregnancy) in the ustekinumab group and 5.7% (4 of 70 subjects) (4 events) (psoriatic arthropathy [2 events], chest pain [1 event], psoriasis [1 event]) in the placebo group, and a causal relationship to study drug could not be denied for 1 event of chest pain and 1 event of psoriatic arthropathy in the placebo group and the outcome of 1 event of psoriasis in the placebo group was reported as unresolved, but other events all resolved.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 36 were 76.3% (58 of 76 subjects) (204 events) in the ustekinumab→placebo group and 63.2% (36 of 57 subjects) (90 events) in the placebo→ustekinumab group[20]. No deaths were reported. The incidences of serious adverse events from Week 12 through Week 36 were 7.9% (6 of 76 subjects) (10 events) in the ustekinumab group (including subjects crossed over from placebo to ustekinumab) and 1.8% (1 of 57 subjects) (1 event) (pelvic mass) in the placebo→ustekinumab group (a subject who did not receive ustekinumab), and a causal relationship to study drug could not be denied for all events, but the outcomes of all events except for haemorrhagic stroke (1 subject) were reported as resolved. The incidence of adverse events leading to treatment discontinuation was 3.9% (3 of 76 subjects) (3 events) (abdominal pain; basal cell carcinoma; and haemorrhagic stroke, 1 subject each) in the ustekinumab group and a causal relationship to study drug could not be denied for all events and the outcomes of all events except for haemorrhagic stroke (1 subject) were reported as resolved.

The incidences of adverse drug reactions through Week 36 were 55.3% (42 of 76 subjects) (111 events) in the ustekinumab→placebo group and 45.6% (26 of 57 subjects) (61 events) in the placebo→ustekinumab group and those reported by ≥5% of subjects in any group were as shown in Table 18.

Table 18. Adverse drug reactions reported by ≥5% of subjects in any group

| Preferred terms | Placebo (Weeks 0-12) | Placebo→Ustekinumab (Weeks 12-36) | Ustekinumab (Weeks 0-36) |
|---|---|---|---|
| Upper respiratory tract infection | 4 (5.7) | 5 (8.8) | 7 (9.2) |
| Nasopharyngitis | 3 (4.3) | 3 (5.3) | 6 (7.9) |
| Influenza | 4 (5.7) | 1 (1.8) | 1 (1.3) |
| Diarrhoea | 1 (1.4) | 1 (1.8) | 4 (5.3) |
| Nausea | 0 | 3 (5.3) | 2 (2.6) |
| Alanine aminotransferase increased | 1 (1.4) | 1 (1.8) | 4 (5.3) |
| Headache | 3 (4.3) | 1 (1.8) | 4 (5.3) |

n (%)

**4.(ii).A.(2).5) Phase III clinical study (5.3.5.1.3, C0743T08 [December 2005 to ongoing (data cut-off of March 2009)])**

A placebo-controlled, randomized, double-blind study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 750 [250 subjects per group]) to evaluate the efficacy

[20] From Week 12 through Week 36, after crossover to ustekinumab.

and safety of ustekinumab and the interim report (through Week 152) (March 2009) of the study was submitted.

Forty-five or 90 mg of ustekinumab or placebo was to be administered subcutaneously according to Figure 2. A long-term extension period began at Week 52 and subjects were to continue to receive the same dose and schedule of ustekinumab that they were receiving at Week 52. Subjects randomized to placebo at Week 40 were to begin retreatment with ustekinumab every 12 weeks at loss of therapeutic effect as assessed by the PASI score.

In Study T04, the PASI 75 response rates at Week 12 in the 45 mg (single dose), 90 mg (single dose), 180 mg (45 mg/week × 4), and 360 mg (90 mg/week × 4) groups were 51.6%, 59.4%, 67.2%, and 81.3%, respectively, and a dose response relationship was observed with approximately 10% increments in PASI 75 response rate observed with every doubling in exposure between 45 mg and 360 mg. Thus, for foreign phase III studies (Studies T08 and T09), "45 or 90 mg of ustekinumab subcutaneously administered at Weeks 0 and 4" corresponding to the medium exposures tested in Study T04 (90 mg and 180 mg) was selected as the initial dosing regimen. Since efficacy peaked at around Week 12 in Study T04, the initial dosing regimen followed by the same dose every 12 weeks was proposed.

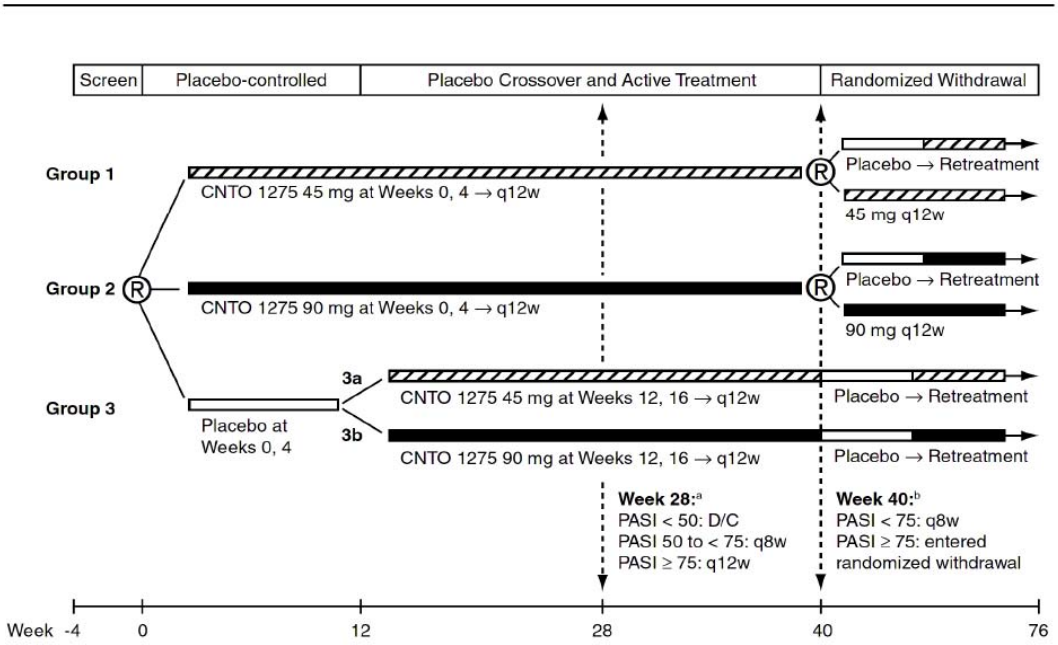



Figure 2. Study design and dosing schedule for Foreign Study T08
Group 1: 45 mg group, Group 2: 90 mg group, Group 3: placebo group, D/C: discontinuation, Ⓡ: randomization, q8w: every 8 weeks, q12w: every 12 weeks, CNTO 1275: ustekinumab
a: At Week 28, in all Groups, nonresponders discontinued study drug, partial responders began q8w dosing, and responders continued q12w dosing.
b: At Week 40, responders to q12w dosing in Groups 1 and 2 were randomized to either placebo or continued q12w ustekinumab (at their original dose) and subjects in Group 3 received placebo. At loss of therapeutic effect, subjects receiving placebo began retreatment (at their dosing regimen prior to Week 40). In all Groups, nonresponders or partial responders began q8w dosing. Subjects receiving q8w dosing continued q8w dosing.

The primary efficacy population included 766 randomized subjects (45 mg group [Group 1 as in Figure 2] 255 subjects; 90 mg group [Group 2 as in Figure 2] 256 subjects; placebo group [Group 3a or 3b as in Figure 2] 255 subjects) while 765 subjects, excluding 1 subject who did not receive study drug (90 mg group), were included in the safety population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 (%) was as shown in Table 19 and the response rate was significantly higher in the ustekinumab groups compared to the placebo group ($P < 0.001$, pairwise comparisons using the Cochran-Mantel-Haenszel $\chi^2$ test). The secondary endpoints of the PASI 50 response rate and the PASI 90 response rate were as shown in Table 19.

Table 19. PASI response rate at Week 12

| | Placebo | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|---|
| PASI 50 response rate | 10.2 (26/255) | 83.5 (213/255) | 85.9 (220/256) |
| PASI 75 response rate | 3.1 (8/255) | 67.1 (171/255) | 66.4 (170/256) |
| PASI 90 response rate | 2.0 (5/255) | 41.6 (106/255) | 36.7 (94/256) |

% (n)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 57.6% (147 of 255 subjects) (302 events) in the 45 mg group, 51.4% (131 of 255 subjects) (269 events) in the 90 mg group, and 48.2% (123 of 255 subjects) (224 events) in the placebo group. No deaths were reported. Serious adverse events were reported by 2 subjects in the 45 mg group (cerebrovascular accident; and hypertension, 1 subject each), 4 subjects in the 90 mg group (herpes zoster disseminated; cellulitis; coronary artery disease; and psoriasis, 1 subject each), and 2 subjects in the placebo group (psychotic disorder; and pneumonia, 1 subject each), and a causal relationship to study drug could not be denied for any of these events except for coronary artery disease, but the outcomes of all events were reported as resolved. The incidences of adverse events leading to treatment discontinuation were 0.4% (1 of 255 subjects) (cerebrovascular accident) in the 45 mg group, 1.6% (4 of 255 subjects) (herpes zoster disseminated; cellulitis; pregnancy; and dyspepsia, 1 subject each) in the 90 mg group, and 2.4% (6 of 255 subjects) (psoriasis [2 subjects], dermatitis exfoliative [2 subjects], psychotic disorder [1 subject], rash generalised [1 subject]) in the placebo group, and a causal relationship to study drug could not be denied for any of these events except for pregnancy, but the outcomes of all events except for pregnancy were reported as resolved.

The incidences of adverse drug reactions were 35.3% (90 of 255 subjects) (163 events) in the 45 mg group, 30.6% (78 of 255 subjects) (162 events) in the 90mg group, and 27.1% (69 of 255 subjects) (125 events) in the placebo group and those reported by ≥2% of subjects in any group were as shown in Table 20.

Table 20. Adverse drug reactions reported by ≥2% of subjects in any group (through Week 12)

| Preferred terms | Placebo | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|---|
| Upper respiratory tract infection | 9 (3.5) | 11 (4.3) | 12 (4.7) |
| Nasopharyngitis | 8(3.1) | 9 (3.5) | 9 (3.5) |
| Headache | 5(2.0) | 12 (4.7) | 11 (4.3) |
| Dizziness | 1 (0.4) | 5 (2.0) | 3 (1.2) |
| Fatigue | 3 (1.2) | 4 (1.6) | 6 (2.4) |
| Injection site erythema | 2 (0.8) | 0 | 7 (2.7) |
| Arthralgia | 6 (2.4) | 4 (1.6) | 6 (2.4) |

n (%)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 152 were 92.1% (348 of 378 subjects) (2481 events) in the 45 mg group[21] and 90.9% (341 of 375 subjects) (2400 events) in the 90 mg group[22]. Two subjects in the placebo→90 mg group (respiratory failure, pneumonia, chronic hepatic failure, and colitis; and completed suicide) and 1 subject in the 90 mg group (intestinal perforation) died, but a causal relationship to study drug was denied for all cases. The incidences of serious adverse events were 7.9% (30 of 378 subjects) in the 45 mg group and 10.1% (38 of 375 subjects) in the 90 mg group, and those reported by ≥2 subjects in either group were coronary artery disease (7 subjects in the 90 mg group), prostate cancer (3 subjects in the 45 mg group), cellulitis (2 subjects in the 90 mg group), osteomyelitis (2 subjects in the 90 mg group), myocardial infarction (2 subjects in the 90 mg group), and cerebrovascular accident (2 subjects in the 45 mg group). The incidences of adverse events leading to treatment discontinuation from Week 0 through Week 152 were 6.9% (26 of 378 subjects) in the 45 mg group and 6.4% (24 of 375 subjects) in the 90 mg group.

The incidences of adverse drug reactions were 62.4% (236 of 378 subjects) (1116 events) in the 45 mg group and 62.9% (236 of 375 subjects) (1073 events) in the 90 mg group and those reported by ≥2% of subjects in either group were as shown in Table 21.

Table 21. Adverse drug reactions reported by ≥2% of subjects in either group (through Week 152)

| Preferred terms | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|
| Nasopharyngitis | 35 (9.3) | 45 (12.0) |
| Upper respiratory tract infection | 69 (18.3) | 64 (17.1) |
| Sinusitis | 21 (5.6) | 18 (4.8) |
| Influenza | 17 (4.5) | 16 (4.3) |
| Gastroenteritis | 19 (5.0) | 14 (3.7) |
| Bronchitis | 16 (4.2) | 15 (4.0) |
| Pharyngitis | 9 (2.4) | 9 (2.4) |
| Urinary tract infection | 10 (2.6) | 7 (1.9) |
| Arthralgia | 27 (7.1) | 19 (5.1) |
| Psoriatic arthropathy | 9 (2.4) | 4 (1.1) |
| Arthritis | 9 (2.4) | 6 (1.6) |
| Back pain | 9 (2.4) | 12 (3.2) |
| Pain in extremity | 6 (1.6) | 8 (2.1) |
| Diarrhoea | 8 (2.1) | 14 (3.7) |
| Oropharyngeal pain | 6 (1.6) | 9 (2.4) |
| Nasal congestion | 5 (1.3) | 8 (2.1) |
| Headache | 29 (7.7) | 22 (5.9) |
| Dizziness | 11 (2.9) | 11 (2.9) |
| Injection site erythema | 14 (3.7) | 19 (5.1) |
| Fatigue | 15 (4.0) | 10 (2.7) |
| Night sweats | 9 (2.4) | 7 (1.9) |
| Cough | 12 (3.2) | 11 (2.9) |
| Alanine aminotransferase increased | 7 (1.9) | 8 (2.1) |
| Insomnia | 8 (2.1) | 8 (2.1) |
| Hypertension | 17 (4.5) | 16 (4.3) |

n (%)

[21] A group of subjects who received 45 mg of ustekinumab by Week 152 (Group 1 and Group 3a). After Week 12 (after crossover to ustekinumab) for Group 3a.

[22] A group of subjects who received 90 mg of ustekinumab by Week 152 (Group 2 and Group 3b). After Week 12 (after crossover to ustekinumab) for Group 3b.

**4.(ii).A.(2).6) Phase III study (5.3.5.1.4, C0743T09 [March 2006 to ongoing (data cut-off of August 2008)])**

A placebo-controlled, randomized, double-blind study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 1200 [400 subjects per group]) to evaluate the efficacy and safety of ustekinumab and the interim report (through Week 100) (August 2008) of the study was submitted.

Forty-five or 90 mg of ustekinumab or placebo was to be administered subcutaneously according to Figure 3. A long-term extension period began at Week 52 and after the unblinding, adjustment of each subject's dosing regimen was allowed at the investigator's discretion. The duration of treatment was up to 264 weeks.

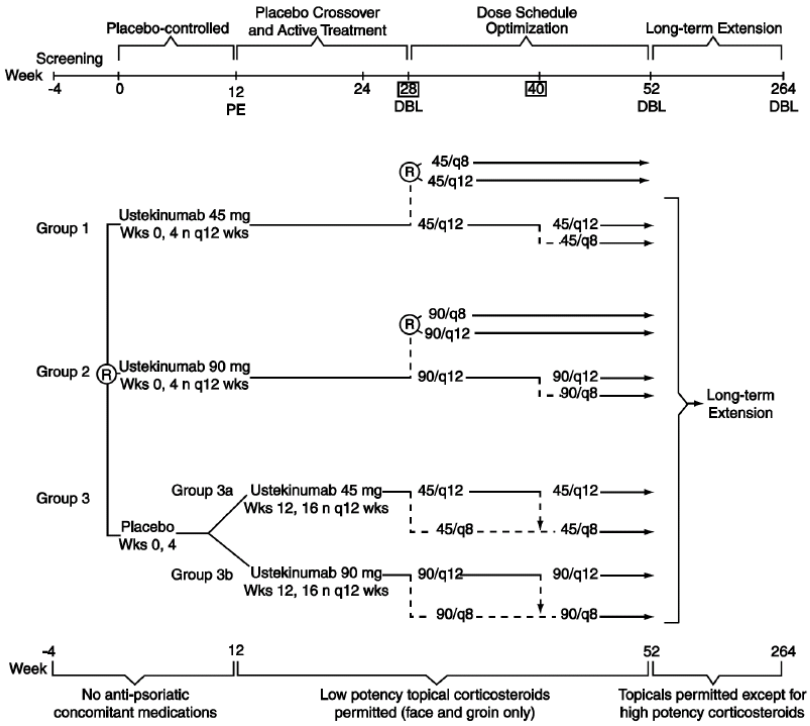



Figure 3. Study design and dosing schedule for Foreign Study T09
Group 1: 45 mg group, Group 2: 90 mg group, Group 3: placebo group, Ⓡ: randomization, PE: primary endpoint, DBL: database lock, q8: every 8 weeks, q12: every 12 weeks.
At Week 28, in all Groups, nonresponders discontinued study treatment. In Groups 1 and 2, partial responders were randomized to either q8wk or q12wk dosing. In Group 3, partial responders began q8wk dosing.
At Week 40, among responders at Week 28 in all Groups, nonresponders and partial responders began q8wk dosing.

The safety population and the primary efficacy population included 1230 randomized subjects (45 mg group [Group 1 as in Figure 3] 409 subjects; 90 mg group [Group 2 as in Figure 3] 411 subjects; placebo group [Group 3a or 3b as in Figure 3] 205 subjects each).

The primary efficacy endpoint of the PASI 75 response rate (%) at Week 12 was as shown in Table 22 and the response rate was significantly higher in the ustekinumab groups compared to the placebo

group ($P < 0.001$, pairwise comparisons using the Cochran-Mantel-Haenszel $\chi^2$ test). The secondary endpoints of the PASI 50 resposne rate and the PASI 90 response rate were as shown in Table 22.

Table 22. PASI response rates at Week 12

| | Placebo | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|---|
| PASI 50 response rate | 10.0 (41/410) | 83.6 (342/409) | 89.3 (367/411) |
| PASI 75 response rate | 3.7 (15/410) | 66.7 (273/409) | 75.7 (311/411) |
| PASI 90 response rate | 0.7 (3/410) | 42.3 (173/409) | 50.9 (209/411) |

% (n)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 53.1% (217 of 409 subjects) (402 events) in the 45 mg group, 48.7% (200 of 411 subjects) (408 events) in the 90 mg group, and 49.8% (204 of 410 subjects) (365 events) in the placebo group. The incidences of serious adverse events were 2.0% (8 of 409 subjects) (intervertebral disc protrusion [2 subjects], angina pectoris; nephrolithiasis; seroma; dactylitis; sciatica; and clavicle fracture, 1 subject each) in the 45 mg group, 1.2% (5 of 411 subjects) (congestive cardiomyopathy; meningioma benign; cellulitis; alcohol withdrawal syndrome; and hypertension, palpitations, ventricular extrasystoles, and vertigo, 1 subject each) in the 90 mg group, and 2.0% (8 of 410 subjects) (cellulitis [2 subjects], hepatic neoplasm malignant and ascites; asthma; cervicobrachial syndrome; chest pain; psoriatic arthropathy; and pityriasis rubra pilaris, 1 subject each) in the placebo group and a causal relationship to study drug could not be denied for any of these events except for intervertebral disc protrusion (2 subjects), angina pectoris, nephrolithiasis, and seroma in the 45 mg group, meningioma benign and alcohol withdrawal syndrome in the 90 mg group, and hepatic neoplasm malignant and ascites; cervicobrachial syndrome; chest pain; and pityriasis rubra pilaris in the placebo group and the outcomes of all events were reported as resolved except for congestive cardiomyopathy (death) in the 90 mg group and hepatic neoplasm malignant and ascites; and psoriatic arthropathy (all unresolved) in the placebo group. The incidences of adverse events leading to treatment discontinuation were 0.2% (1 of 409 subjects) (1 event) (neutropenia) in the 45 mg group, 1.5% (6 of 411 subjects) (10 events) (pneumonia; basal cell carcinoma; hepatitis; meningioma benign; hypertension, palpitations, ventricular extrasystoles, and vertigo; and alcohol abuse and alcohol withdrawal syndrome, 1 subject each) in the 90 mg group, and 1.7% (7 of 410 subjects) (7 events) (psoriasis [2 subjects], pustular psoriasis; cellulitis; pregnancy; ascites; and psoriatic arthropathy, 1 subject each) in the placebo group, and a causal relationship to study drug could not be denied for all events except for pregnancy and ascites in the placebo group and basal cell carcinoma; meningioma benign; and alcohol abuse and alcohol withdrawal syndrome in the 90 mg group and the outcomes of all events except for ascites, pustular psoriasis, and psoriatic arthropathy in the placebo group were reported as resolved.

The incidences of adverse drug reactions (including abnormal laboratory test values) were 34.5% (141 of 409 subjects) in the 45 mg group, 32.8% (135 of 411 subjects) in the 90 mg group, and 29.5% (121 of 410 subjects) in the placebo group and those reported by ≥2% of subjects in any group were as shown in Table 23.

Table 23. Adverse drug reactions reported by ≥2% of subjects in any group (through Week 12)

| Preferred terms | Placebo | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|---|
| Nasopharyngitis | 18 (4.4) | 15 (3.7) | 13 (3.2) |
| Upper respiratory tract infection | 8 (2.0) | 10 (2.4) | 7 (1.7) |
| Diarrhoea | 8 (2.0) | 7 (1.7) | 10 (2.4) |
| Headache | 12 (2.9) | 19 (4.6) | 13 (3.2) |
| Fatigue | 8 (2.0) | 11 (2.7) | 10 (2.4) |
| Arthralgia | 5 (1.2) | 12 (2.9) | 8 (1.9) |

n (%)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 100 were 90.4% (548 of 606 subjects) (2883 events) in the 45 mg group[23] and 90.4% (548 of 606 subjects) (2956 events) in the 90 mg[24] group. One subject in the placebo→45 mg group (aspiration), 1 subject in the placebo→90 mg group (metastatic renal cancer), and 2 subjects in the 90 mg group (shock, congestive cardiomyopathy) died and a causal relationship to study drug was denied for all events except for congestive cardiomyopathy. The incidences of serious adverse events were 10.1% (61 of 606 subjects) in the 45 mg group and 9.2% (56 of 606 subjects) in the 90 mg group and those reported by ≥2 subjects in either group were as shown in Table 24. The incidences of serious adverse events for which a causal relationship to study drug could not be denied were 2.5% (15 of 606 subjects) in the 45 mg group and 2.6% (16 of 606 subjects) in the 90 mg group. The incidences of adverse events leading to treatment discontinuation were 3.3% (20 of 606 subjects) in the 45 mg group and 5.4% (33 of 606 subjects) in the 90 mg group.

The incidences of adverse drug reactions (including abnormal laboratory test values) were 62.9% (381 of 606 subjects) in the 45 mg group and 63.7% (386 of 606 subjects) in the 90 mg group, and those reported by ≥2% of subjects in either group were as shown in Table 25.

Table 24. Serious adverse events reported by ≥2 subjects in either group (through Week 100)

| Preferred terms | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|
| Coronary artery disease | 4 (0.7) | 1 (0.2) |
| Angina unstable | 2 (0.3) | 2 (0.3) |
| Myocardial infarction | 2 (0.3) | 1 (0.2) |
| Prostate cancer | 1 (0.2) | 2 (0.3) |
| Cellulitis | 2 (0.3) | 1 (0.2) |
| Diverticulitis | 1 (0.2) | 2 (0.3) |
| Abdominal pain | 2 (0.3) | 0 |
| Chest pain | 2 (0.3) | 6 (1.0) |
| Nephrolithiasis | 3 (0.5) | 1 (0.2) |
| Renal colic | 1 (0.2) | 2 (0.3) |
| Intervertebral disc protrusion | 4 (0.7) | 0 |

n (%)

Table 25. Adverse drug reactions reported by ≥2% of subjects in either group (through Week 100)

| Preferred terms | Ustekinumab 45 mg | Ustekinumab 90 mg |
|---|---|---|
| Nasopharyngitis | 93 (15.3) | 101 (16.7) |
| Upper respiratory tract infection | 96 (15.8) | 90 (14.9) |
| Influenza | 34 (5.6) | 38 (6.3) |
| Bronchitis | 28 (4.6) | 23 (3.8) |
| Sinusitis | 20 (3.3) | 27 (4.5) |
| Gastroenteritis | 23 (3.8) | 21 (3.5) |
| Pharyngitis | 7 (1.2) | 12 (2.0) |
| Urinary tract infection | 9 (1.5) | 13 (2.1) |
| Oral herpes | 13 (2.1) | 7 (1.2) |

[23] A group of subjects who received 45 mg of ustekinumab by Week 100 (Group 1 and Group 3a).

[24] A group of subjects who received 90 mg of ustekinumab by Week 100 (Group 2 and Group 3b).

| | | |
|---|---|---|
| Back pain | 19 (3.1) | 25 (4.1) |
| Arthralgia | 33 (5.4) | 36 (5.9) |
| Myalgia | 11 (1.8) | 14 (2.3) |
| Pain in extremity | 13 (2.1) | 10 (1.7) |
| Skeletal muscle pain | 12 (2.0) | 6 (1.0) |
| Chest pain | 4 (0.7) | 17 (2.8) |
| Diarrhoea | 25 (4.1) | 23 (3.8) |
| Pruritus | 11 (1.8) | 16 (2.6) |
| Night sweats | 5 (0.8) | 14 (2.3) |
| Fatigue | 24 (4.0) | 20 (3.3) |
| Injection site erythema | 22 (3.6) | 25 (4.1) |
| Headache | 46 (7.6) | 38 (6.3) |
| Dizziness | 10 (1.7) | 16 (2.6) |
| Cough | 22 (3.6) | 27 (4.5) |
| Pharyngolaryngeal pain | 14 (2.3) | 20 (3.3) |
| Hypertension | 25 (4.1) | 29 (4.8) |

n (%)

## *4.(ii).B Outline of the review*

### 4.(ii).B.(1) Efficacy

#### 4.(ii).B.(1).1) Efficacy in the treatment of psoriasis vulgaris and plaque psoriasis in psoriatic arthritis

PMDA concludes that based on the submitted study data, the efficacy of ustekinumab in the treatment of psoriasis vulgaris and plaque psoriasis in psoriatic arthritis has been demonstrated.

#### 4.(ii).B.(1).2) Efficacy of ustekinumab in reducing joint symptoms of psoriatic arthritis

While the treatment of joint symptoms as well as skin symptoms is considered important in psoriatic arthritis, pain VAS assessment only was performed in Japanese Study JPN-02 and the efficacy of ustekinumab in reducing joint symptoms has not been confirmed overseas either. PMDA asked the applicant to explain their view on the expected degree of efficacy of ustekinumab in reducing joint symptoms.

The applicant explained as follows:

In Japanese Study JPN-02, 22 subjects who were confirmed by the investigator or sub-investigator to have joint symptoms at Week 0 (3 subjects in the placebo group, 6 subjects in the 45 mg group, 13 subjects in the 90 mg group) were assessed for pain VAS score. As a result, the median changes from baseline at Week 12 (mean ± SD) were 1.0 (8.0 ± 13.00) in the placebo group, -41.0 (-38.5 ± 28.93) in the 45 mg group, and -10.0 (-9.3 ± 18.23) in the 90 mg group, and ustekinumab tended to reduce joint pain, though the number of subjects assessed was small. In a foreign phase II clinical study that evaluated the efficacy of ustekinumab in reducing the symptoms and signs of arthritis in patients with active psoriatic arthritis (Study T10), the primary endpoint of the ACR 20 response rate at Week 12 was significantly higher in the ustekinumab group (42.1% [32 of 76 subjects]) compared to the placebo group (14.3% [10 of 70 subjects]) ($P < 0.001$, Cochran-Mantel-Haenszel $\chi 2$ test), suggesting the efficacy of ustekinumab in reducing joint symptoms. These results are not substantially different from the results from adalimumab or infliximab foreign phase II and III studies in patients with active psoriatic arthritis (Table 26).

Table 26. Comparison of efficacy of ustekinumab vs. other biologics
based on foreign placebo-controlled, double-blind studies in patients with psoriatic arthritis

| Summary of study | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Product | Ustekinumab | | | Infliximab | | | | Adalimumab | | | |
| Study ID | Foreign phase II clinical study (C0743T10) | | | Phase II clinical study (IMPACT) | | Phase III clinical study (IMPACT2) | | Phase III clinical study (Study M02-518) | | Phase III clinical study (Study M02-570) | |
| Main dosing regimen | ustekinumab 90 mg (63 mg)* or placebo subcutaneously administered at Weeks 0, 1, 2, and 3 and then crossover to placebo or ustekinumab 90 mg (63 mg) subcutaneously administered at Weeks 12 and 16 | | | infliximab 5 mg/kg or placebo given as an intravenous infusion at Weeks 0, 2, 6, and 14 | | infliximab 5 mg/kg or placebo given as an intravenous infusion at Weeks 0, 2, 6, 14, and 22 | | adalimumab 40 mg or placebo subcutaneously administered every other week | | adalimumab 40 mg or placebo subcutaneously administered every other week | |
| Primary endpoint | ACR 20 response rate (Week 12) | | | ACR 20 response rate (Week 16) | | ACR 20 response rate (Week 14) | | ACR 20 response rate (Week 12) | | ACR 20 response rate (Week 12) | |
| Study results | | | | | | | | | | | |
| Treatment group | Placebo | Ustekinumab 90 mg (63 mg) | Placebo →90 mg (63 mg)[a] | Placebo | infliximab 5 mg/kg | Placebo | infliximab 5 mg/kg | Placebo | adalimumab 40 mg | Placebo | adalimumab 40 mg |
| Number of subjects | 70 | 76 | 55 | 52 | 52 | 100 | 100 | 162 | 151 | 49 | 51 |
| ACR 20 response rate | 14.3% | 42.1% | 50.9% | 9.6% | 65.4% | 11.0% | 58.0% | 14% | 58% | 16% | 39% |
| Pain VAS score (SD) | -13.17 (62.141) [b] | 21.38 (65.579) [b] | 29.23 (49.817) [b] | -8.7 (7.8) [b] | 53.7 (7.7) [b] | -11.8 (109.8) [b] | 39.6 (56.1) [b] | — | — | 0.2 (23.1) [c] | -15.4 (25.6) [c] |

a: Assessment at Week 24 (12 weeks after crossover to ustekinumab) for subjects crossed over from placebo to ustekinumab at Week 12,
b: mean percent improvement (SD), c: mean change (SD)
* During this clinical study, it was revealed that the vials of another study drug that was not used in this study contained particulate matters. Since the lyophilized formulation of ustekinumab used in this study was also filled at the same site over the same period of time, as a precautionary measure to ensure subject's safety, the prepared solution for injection was filtered (pore size, 0.22 μm). The volume of the filtered solution for injection was approximately 0.70 mL (corresponding to 63 mg of ustekinumab).

Furthermore, in Study T10 and foreign studies of adalimumab and infliximab, changes in pain VAS score were measured as an ACR core set variable. As a result, as shown in Table 26, improvement in joint pain as measured by pain VAS score as well as improvement in joint symptoms as measured by the primary endpoint of the ACR 20 response rate was observed simultaneously in all studies. Based on the above, though pain VAS assessment only was performed in Japanese Study JPN-02, the efficacy of ustekinumab in reducing joint symptoms can be expected also in Japanese patients with psoriatic arthritis.

The applicant also responded as follows:
Two foreign phase III studies to confirm the efficacy of ustekinumab (45 mg and 90 mg) in improving the symptoms and signs of arthritis and preventing joint structural damage progression in patients with active psoriatic arthritis are currently ongoing.

In Japanese Study JPN-02, subjects with joint symptoms at Week 0, regardless of a diagnosis of psoriatic arthritis, were assessed for pain VAS score. PMDA asked the applicant to also explain the results from subjects diagnosed with psoriatic arthritis.

The applicant explained as follows:

Usually, patients who develop psoriatic arthritis have skin symptoms of psoriasis first, followed by joint symptoms several years later and the statistics of psoriasis patients in Japan report that only 1.0% of the patients are diagnosed with psoriatic arthritis at the first visit (Hashimoto Y. *Dermatology Practice 16 Psoriasis*. 2004;215-9). Based on patients registered with the Japanese Society for Psoriasis Research from 1999 to 2002 (4 years), 2.0% of the patients were diagnosed with psoriatic arthritis at the first visit while 7.6% of the patients had joint symptoms. Taking account of these findings, subjects who were confirmed by the investigator or sub-investigator to have joint symptoms, regardless of a diagnosis of psoriatic arthritis, were assessed for pain VAS score in Japanese Study JPN-02. Of 14 subjects with a diagnosis of psoriatic arthritis enrolled in Study JPN-02, 12 subjects had joint symptoms at Week 0 and were assessed for pain VAS score (1 subject in the placebo group, 4 subjects in the 45 mg group, 7 subjects in the 90 mg group). In these 12 subjects, the percent improvement in pain VAS score from baseline to Week 12 was -2.8% in the 1 subject in the placebo group and the median values (mean ± SD) in the 45 mg and 90 mg groups were 53.00% (27.19 ± 78.451) and 41.67% (29.88 ± 40.205), respectively. Though the number of subjects assessed was limited, like the results from 22 subjects with joint symptoms, these results have suggested that ustekinumab improves joint pain.

PMDA considers as follows:

As there are a limited number of patients with psoriatic arthritis in Japan, it is understandable that it was difficult to conduct a Japanese clinical study to confirm the efficacy of ustekinumab in reducing joint symptoms. Meanwhile, Japanese Study JPN-02 should have been designed to allow for certain assessment of joint symptoms as well. For example, patients diagnosed with psoriatic arthritis should have been enrolled in the study and balanced across treatment groups for assessment of joint symptoms and the ACR response rates etc. should have also been assessed with a view to comparison with foreign study data. On the other hand, the results from a foreign phase II study, though not a confirmatory study, have suggested the efficacy of ustekinumab in reducing joint symptoms as assessed by the ACR criteria, the results from Japanese Study JPN-02 have shown a trend toward improvement in pain VAS score though in a small number of subjects, and foreign clinical studies of ustekinumab and existing biologics have suggested similar trends in the ACR 20 response rate and pain VAS score. Taking account of these findings, the efficacy of ustekinumab in reducing joint symptoms can be expected also in Japanese patients with psoriatic arthritis and there should be no major problems in the assessment of joint symptoms in the Japanese clinical study. However, as data in Japanese patients with psoriatic arthritis are very limited, data concerning joint symptoms should be obtained wherever possible via post-marketing surveillance, arranging for patients who have mainly joint symptoms and see rheumatologists etc. to be assessed also for disease activity as measured by the ACR core set or DAS, and the information including foreign data on the inhibition of structural damage progression etc., which will become available in future, should be provided appropriately to healthcare providers in clinical settings.

**4.(ii).B.(2) Dosage and administration**

**4.(ii).B.(2).1) Dosage and administration**

**4.(ii).B.(2).1).(a) Usual dose**

In Japanese Study JPN-02, although the primary endpoint of the PASI 75 response rate at Week 12 tended to be higher in the 90 mg group (67.7%) compared to the 45 mg group (59.4%), the PASI 50 response rate was almost the same in the 45 mg group (82.8%) and the 90 mg group (83.9%), which indicated that both dose levels of ustekinumab can achieve clinically significant improvement in skin lesions in most patients, etc. Thus, a usual dose of 45 mg of ustekinumab has been proposed.

PMDA concluded that there is no particular problem with the proposed usual dose of 45 mg of ustekinumab, which can be expected to produce a clinical response in most psoriasis patients.

**4.(ii).B.(2).1).(b) An increased dose of 90 mg**

In Foreign Studies T08 and T09, serum ustekinumab concentrations decreased with increasing body weight and the PASI 75 response rate also tended to be lower, and there were differences in efficacy between the 45 mg and 90 mg groups in subjects weighing >100 kg, and the PASI 75 response rate and the trough serum concentration of ustekinumab, etc. in subjects weighing >100 kg in the 90 mg group were comparable to those in subjects weighing ≤100 kg in the 45 mg group. On the basis of these findings, among others, in foreign countries including the US and the EU, the recommended dose of ustekinumab is 45 mg for psoriasis patients weighing ≤100 kg and 90 mg for psoriasis patients weighing >100 kg. Also in Japanese Study JPN-02, serum ustekinumab concentrations decreased with increasing body weight and the PASI 75 response rate also tended to be lower, suggesting that subjects weighing >100 kg tended to have lower serum ustekinumab concentrations. The pharmacokinetics of ustekinumab are considered similar between Japanese and foreign patients of the same body weight range and it is predicted that a dose response relationship as seen in the foreign studies occurs in subjects weighing >100 kg. Therefore, also in Japan, the following statement has been included in the proposed dosage and administration section: “A 90 mg dose may be used in patients weighing >100 kg”.

However, only 6 subjects weighing >100 kg were enrolled in the Japanese study and there is no sufficient evidence supporting the use of a 90 mg dose in this patient population. In addition, Japanese patients weighing >100 kg are uncommon. Taking account of these points, PMDA considers that the proposed dosing instruction is not appropriate.

On the other hand, in Japanese Study JPN-02, the PASI 75 response rate and PASI 90 response rate at Week 12 in the 90 mg group were 8.3% and 10.7% higher, respectively, than those in the 45 mg group and ≥10% higher response rates were observed consistently also after Week 28 and there were no major differences in safety between the two groups. Furthermore, in Study JPN-02 (at Week 28), 33.3% of subjects in the 45 mg group and 17.5% of subjects in the 90 mg group had trough serum ustekinumab concentrations less than the lower limit of quantification (0.17 μg/mL) and this

proportion was rather high, especially in the 45 mg group, and the PASI 75 response rate in subjects with trough serum ustekinumab concentrations less than the lower limit of quantification was approximately 30% lower than that in subjects with trough serum ustekinumab concentrations of ≥0.17 μg/mL to <0.40 μg/mL [see "4.(i) Summary of clinical pharmacology studies"]. Taking account of these findings, the lack of efficacy in a certain number of subjects due to insufficient serum ustekinumab concentrations is expected at a dose of 45 mg, regardless of body weight (>100 kg). Therefore, in Japan, a dose increase should be recommended as follows: "If the effect of a 45 mg dose is insufficient, a dose of 90 mg may be used."

Since a dose increase may be attempted also in nonresponders to ustekinumab, etc., symptoms over time after the dose increase should be monitored closely and it is necessary to adequately advise against continuing high-dose ustekinumab without careful consideration in patients in whom no effects of the increased dose of ustekinumab are noted. The efficacy and safety of an increased dose of ustekinumab need to be fully investigated via post-marketing surveillance.

**4.(ii).B.(2).2) Possibility of withdrawal from ustekinumab therapy etc. after remission**

PMDA asked the applicant to explain their view on the possibility of withdrawal of therapy after remission with ustekinumab or the possibility of intermittent administration (treatment interruption with reintroduction as needed) etc.

The applicant explained as follows:

In Foreign Study T08, (a) responders at Week 40 (subjects with a ≥75% improvement in PASI score) were re-randomized to maintenance therapy or withdrawal of therapy and the time to loss of PASI 75 response was assessed. In subjects re-randomized to withdrawal of therapy, the PASI 75 response rate decreased over time and was 63% at Week 52 (12 weeks after treatment withdrawal) and 70.3% of the subjects had an increase in PGA score of ≥1 at Week 52 and (b) furthermore, the percent improvement in PASI score over time after treatment withdrawal in responders at Week 40 re-randomized to placebo (i.e. treatment withdrawal) was assessed according to the percent improvement in PASI score at Week 40 (≥75% to <90% [32 subjects in the 45 mg group, 45 subjects in the 90 mg group] vs. ≥90% [109 subjects in the 45 mg group, 134 subjects in the 90 mg group]). The mean and median percent improvements in PASI scores were less than 75% at Weeks 48 to 52 in subjects with a ≥75% to <90% improvement at Week 40 and less than 75% at Week 60 even in subjects with a ≥90% improvement at Week 40, suggesting that it is not true that PASI response is maintained for a long time in subjects who showed a higher percent improvement in PASI score. Based on these results, continuous administration of ustekinumab is recommended.

PMDA considers as follows:

Given that ustekinumab is associated with the risk of serious adverse reactions, the amount of ustekinumab used should be minimized. As patients with prolonged remission etc. may be studied, a more detailed investigation concerning treatment withdrawal and intermittent administration as needed

etc. should be performed in future. It is important to investigate symptoms over time etc. in patients after treatment withdrawal and patients retreated after withdrawal from therapy etc. and collect sufficient information, also after the product launch.

**4.(ii).B.(3) Indications and clinical positioning etc.**

**4.(ii).B.(3).1) Indications**

PMDA considers as follows:

The confirmatory study of ustekinumab was designed to enrollpatients regardless of prior medication use, etc. and was conducted on the assumption that ustekinumab would be used even as a first-line drug for patients resistant to local therapy (i.e. as an equal option to phototherapy or conventional systemic therapy such as cyclosporine and etretinate). Psoriasis is not generally a fatal disease while ustekinumab, as with adalimumab and infliximab (other biologics approved for psoriasis), increases the risk of serious infections etc. which may run a fatal course, and the long-term safety of ustekinumab including the risk of malignancy has not fully been elucidated. Taking account of these points, it is not appropriate to position ustekinumab as an equal option to phototherapy or conventional systemic therapy and ustekinumab should rather be positioned as a treatment, like the approved biologics, for patients who have had an inadequate response or intolerance to phototherapy or conventional systemic therapy, etc.

PMDA asked the applicant to present the results of subgroup analyses of patients who were considered to have an inadequate response to phototherapy or cyclosporine or etretinate. As described below, the applicant responded that there were no major differences in the efficacy and safety of ustekinumab between the subgroups and the overall population.

Although the response to prior therapy for psoriasis was not reported in Japanese Study JPN-02, given that the study included patients with moderate to severe psoriasis, it is inferred that the majority of the subjects failed to respond adequately to prior therapy. Thus, subgroup analyses were performed according to previous experience with cyclosporine, etretinate or phototherapy. As a result, regarding efficacy, the PASI 75 response rates among subjects with previous experience with cyclosporine, etretinate, or phototherapy were 59.6% (31 of 52 subjects) in the 45 mg group, 67.2% (39 of 58 subjects) in the 90 mg group, and 0% (0 of 25 subjects) in the placebo group, which were almost comparable to those in the overall population (59.4% in the 45 mg group, 67.7% in the 90 mg group, 6.5% in the placebo group). Also when subgroups were analyzed according to previous experience with each of cyclosporine, etretinate, and phototherapy, there were no major differences in the results between each of the subgroups and the overall population, though the number of subjects of each subgroup was small. Regarding safety, overall adverse events, serious adverse events, adverse events leading to treatment discontinuation, and serious infections were analyzed according to previous experience with each of cyclosporine, etretinate, and phototherapy. As a result, the incidences of adverse events by treatment group were similar, regardless of previous experience with each of these therapies.

Furthermore, as the response to prior therapy was reported in Foreign Studies T08 and T09, a subgroup analysis of subjects who had an inadequate response to cyclosporine, acitretin (an oral retinoid, unapproved in Japan), or phototherapy was performed. The PASI 75 response rates at Week 12 in the 45 mg, 90 mg, and placebo groups were 66.8% (181 of 271 subjects), 70.1% (162 of 231 subjects), and 2.2% (6 of 267 subjects), respectively, which were almost comparable to those in the overall population (66.9% in the 45 mg group, 72.1% in the 90 mg group, 3.5% in the placebo group). There were also no major differences in safety between the subgroup of subjects who had an inadequate response to cyclosporine, acitretin, or phototherapy and the overall population.

Based on the above, PMDA considers as follows:
The indication statement should be modified as shown below and the following statements should be included in the precautions for indications section of the package insert: ustekinumab should be used in (a) patients with a body surface area involvement of ≥10% who have had an inadequate response to conventional systemic therapy (including UV-light therapy) or (b) patients with refractory skin or joint symptoms. In addition, the use of ustekinumab should be limited to physicians who are familiar with the diagnosis and treatment of psoriasis to ensure that a correct diagnosis is made, that appropriate patients are selected, and that the proper use is complied with.

[Indications]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris, Psoriatic arthritis

Given that ustekinumab has been demonstrated to be highly effective in the treatment of plaque psoriasis etc. and that its mechanism of action is different from conventional therapy, ustekinumab is expected to play an important role in the treatment of psoriasis. In order to prevent ustekinumab from being used improperly, it is important that the use of ustekinumab is determined carefully based on its risks and benefits and that patients themselves also fully understand the risks of ustekinumab and comply with its proper use.

**4.(ii).B.(3).2) Positioning of ustekinumab relative to existing biologics**
While both adalimumab and infliximab (other biologics approved for the treatment of psoriasis) neutralize the biological activity of human TNF-α, ustekinumab binds to human IL-12 and IL-23 and neutralizes their biological activities. Ustekinumab has a novel mechanism of action. PMDA asked the applicant to explain their view on the positioning of ustekinumab relative to the existing biologics.

The applicant explained as follows:
No head to head efficacy studies of ustekinumab vs. adalimumab or infliximab have been performed in Japan or overseas.Adalimumab and infliximab were approved for the indication of psoriasis in

Japan in January 2010 and there is limited clinical experience with these biologics in Japanese psoriasis patients at present. Thus, it is difficult to define the positioning of ustekinumab relative to these drugs. Compared to these drugs, ustekinumab has the following characteristics: (a) Comparison of the results of Japanese clinical studies indicates that the efficacy of ustekinumab in treating psoriatic skin lesions is as high as that of adalimumab or infliximab (Table 27), (b) The safety databases, which include Japanese and foreign data, have shown a favorable safety profile of ustekinumab and there should be no particular safety concerns about ustekinumab compared to anti-TNF agents at present, and (c) Psoriasis has a chronic nature, which often requires long-term treatment, while the effect of ustekinumab is maintained by subcutaneous injections every 12 weeks and ustekinumab requires lower dosing frequency and is easier to use, compared to adalimumab and infliximab. Furthermore, ustekinumab has a novel mechanism of action and the results from foreign phase III studies have suggested the efficacy of ustekinumab also in subjects who have discontinued other biologic therapy due to an inadequate response. There have been no safety concerns about the use of ustekinumab, even in subjects who have discontinued other biologic therapy due to intolerance (Tables 28 and 29). Taking account of these findings, ustekinumab is expected to possibly offer another therapeutic option for patients who do not respond to adalimumab or infliximab or those who cannot use adalimumab or infliximab for safety reasons.

Table 27. Comparison of efficacy of ustekinumab vs. other biologics
based on Japanese placebo-controlled, double-blind studies in psoriasis patients

| Non-proprietary name | Ustekinumab | | Adalimumab[a] | | Infliximab[a] | |
|---|---|---|---|---|---|---|
| Psoriasis severity | PASI ≥12<br>BSA ≥10% | | PASI ≥12<br>BSA ≥10% | | PASI ≥12<br>BSA ≥10% | |
| Dosing regimen during the placebo-controlled period | 45 mg, 90 mg, or placebo administered at Weeks 0 and 4 | | 40 mg, 80 mg, or placebo administered every other week (including loading dose of 80 mg followed by 40 mg given every other week) | | 5 mg/kg or placebo intravenously administered at Weeks 0, 2, and 6 | |
| Primary endpoint | PASI 75 response rate at Week 12 | | PASI 75 response rate at Week 16 | | PASI 75 response rate at Week 10 | |
| PASI 75 response rate at the proposed or approved dosing regimen | Placebo | 45 mg | Placebo | 80 mg loading dose + 40 mg | Placebo | 5 mg/kg |
| | 6.5%<br>(2/31 subjects) | 59.4%<br>(38/64 subjects) | 4.3%<br>(2/46 subjects) | 62.8%<br>(27/43 subjects) | 0%<br>(0/19 subjects) | 68.6%<br>(24/35 subjects) |

a: Cited from the disclosed CTD and the package insert

Table 28. PASI 50, PASI 75, and PASI 90 response rates (Week 12) in subjects previously treated with other biologics

| | Pooled data from Studies T08 and T09 | | |
|---|---|---|---|
| | Placebo | 45 mg | 90 mg |
| Patients who have discontinued other biologic therapy (etanercept, infliximab, adalimumab, alefacept, efalizumab) due to an inadequate response (n) | 104 | 81 | 106 |
| PASI 90 response rate | 1<br>(1.0%) | 32<br>(39.5%) | 38<br>(35.8%) |
| PASI 75 response rate | 2<br>(1.9%) | 47<br>(58.0%) | 70<br>(66.0%) |
| PASI 50 response rate | 7<br>(6.7%) | 63<br>(77.8%) | 86<br>(81.1%) |

n (%)

Table 29. Overview of adverse events in subjects who inadequately responded to or were intolerant to other biologic therapies (through Week 12) (Pooled data from Studies T08 and T09)

| | Overall population | | | Patients who inadequately responded to other biologic therapies | | | Patients who were intolerant to other biologic therapies | | |
|---|---|---|---|---|---|---|---|---|---|
| Treatment group | Placebo | 45 mg | 90 mg | Placebo | 45 mg | 90 mg | Placebo | 45 mg | 90 mg |
| No. of patients treated | 665 | 664 | 666 | 104 | 81 | 106 | 25 | 21 | 26 |
| Mean evaluation period (weeks) | 12.0 | 12.2 | 12.2 | 11.9 | 12.2 | 12.2 | 12.3 | 12.2 | 12.1 |
| Patients with adverse events | 324 (48.7) | 361 (54.4) | 328 (49.2) | 54 (51.9) | 40 (49.4) | 56 (52.8) | 14 (56.0) | 14 (66.7) | 13 (50.0) |
| Patients with serious adverse events | 10 (1.5) | 10 (1.5) | 9 (1.4) | 0 (0.0) | 1 (1.2) | 2 (1.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Patients with adverse events leading to treatment discontinuation | 13 (2.0) | 2 (0.3) | 10 (1.5) | 4 (3.8) | 0 (0.0) | 1 (0.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Patients with serious infections | 3 (0.5) | 0 (0.0) | 3 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

n (%)

PMDA considers as follows:

Although there is no objection to the applicant's view that the efficacy of ustekinumab in treating psoriatic skin lesions is as high as that of adalimumab or infliximab, the effect on joint symptoms is also important when considering the positioning of different biologics in the treatment of psoriasis and the positioning of ustekinumab needs to be further discussed, taking also account of the data on its effect in preventing the progression of joint damage, etc., which will be obtained from foreign studies. Regarding safety, as there is limited clinical experience with ustekinumab in Japan and overseas, it is necessary to collect sufficient information via post-marketing surveillance etc. and then determine the risk-benefit balance of ustekinumab and the consequent positioning of ustekinumab. Based on the novel mechanism of action of ustekinumab and foreign data, ustekinumab is expected to be useful also in patients who have responded inadequately to existing biologics. However, as no relevant Japanese data are available, it is necessary to investigate it via post-marketing surveillance etc. and provide the information to healthcare providers in clinical settings. On the other hand, the efficacy of other biologics in patients who have responded inadequately to ustekinumab has not so far been studied overseas or in Japan and such data will also be important for defining the positioning of biologics (choice between different biologics) and this is an issue for a future investigation.

**4.(ii).B.(3).3) Concomitant use with conventional systemic therapy and switching from other biologics to ustekinumab**

PMDA considers as follows:

Although it is envisaged that ustekinumab may be used in combination with systemic therapy such as cyclosporine and etretinate or phototherapy for refractory cases etc., there are no sufficient data regarding these combinations. Especially, when ustekinumab is used in combination with immunosuppressive systemic therapy, the possibility of developing infections or malignancies due to enhanced immunosuppression cannot be ruled out, and when ustekinumab is used in combination with phototherapy, the possibility of an increased risk of skin cancer cannot be excluded either. Thus, the package insert etc. should advise that the safety of ustekinumab in combination with other systemic therapy or phototherapy has not been established, so that the risks and benefits of such combination therapy will be determined carefully after consideration of the safety of each therapy.

Although there is no specific evidence about the concomitant use of ustekinumab with other biologics that affect the immune system, it is desiable to avoid the use of ustekinumab in combination with other biologics, as it has been reported that the use of a combination of different biologics resulted in an increased incidence of serious infections in patients with rheumatoid arthritis. Likewise, also when switching from other biologics to ustekinumab is carried out, adequate caution should be exercised against the possible development of serious infections etc. and such precaution statement should also be included in the package insert etc.

Furthermore, it is necessary to carefully investigate, also in the post-marketing surveillance, the actual state of concomitant use with systemic therapy or phototherapy (proportion, patient background, duration of concomitant use, etc.), the safety and efficacy of the concomitant use, the actual state of switching from other biologics (proportion, patient background, washout period, etc.), and the safety and efficacy of the switching to ustekinumab, etc., and provide the obtained information to medical practice as appropriate to promote the proper use of ustekinumab.

**4.(ii).B.(4) Safety**

**4.(ii).B.(4).1) Overview of safety**

Adverse events during the placebo-controlled period through Week 12 and during the treatment period through Week 72 in Japanese Study JPN-02, and during the placebo-controlled period through Week 12 and during the entire reporting period in pooled 3 foreign psoriasis studies (T04, T08, T09) are summarized in Table 30 and Table 31, respectively.

Table 30. Adverse events in Japanese study

| | Study JPN-02 | | | |
|---|---|---|---|---|
| | (Through Week 12) | | | (Through Week 72) |
| | Ustekinumab | | Placebo (N = 32) | Combined ustekinumab (N = 154) |
| | 45 mg (N = 64) | 90 mg (N = 62) | | |
| Deaths | 0 | 0 | 0 | 0 |
| Serious adverse events | 0 | 3 (4.8) | 2 (6.3) | 13 (8.4) |
| Serious adverse events leading to treatment discontinuation | 0 | 3 (4.8) | 1 (3.1) | 6 (3.9) |
| Serious adverse events related to study drug | 0 | 3 (4.8) | 1 (3.1) | 8 (5.2) |
| All adverse events | 42 (65.6) | 37 (59.7) | 21 (65.6) | 150 (97.4) |
| Adverse events leading to treatment discontinuation | 0 | 4 (6.5) | 2 (6.3) | 6 (3.9) |
| Adverse events related to study drug | 35 (54.7) | 28 (45.2) | 19 (59.4) | 136 (88.3) |

n (%)

Table 31. Adverse events in pooled 3 foreign psoriasis studies

| | Studies T04, T08, and T09 | | | | |
|---|---|---|---|---|---|
| | Through Week 12 | | | | Entire reporting period [a] |
| | Ustekinumab | | | Placebo (N = 732) | Combined ustekinumab (N = 2266) |
| | 45 mg (N = 790) | 90 mg (N = 792) | Combined ustekinumab (N = 1582) | | |
| Deaths | 0 | 1 (0.1) | 1 (0.1) | 0 | 1 (0.04) |
| Serious adverse events | 13 (1.6) | 11 (1.4) | 24 (1.5) | 10 (1.4) | 75 (3.3) |
| All adverse events | 455 (57.6) | 409 (51.6) | 864 (54.6) | 369 (50.4) | 1676 (74.0) |
| Adverse events leading to treatment discontinuation | 9 (1.1) | 11 (1.4) | 20 (1.3) | 14 (1.9) | 57 (2.5) |

n (%)
a: Data through Week 36 from Study T04, data through Week 52 from Study T08, and data through Week 28 from Study T09 were pooled for the table.

In Japanese Study JPN-02, there were no major differences in the incidence of adverse events during the placebo-controlled period through Week 12 among the placebo, 45 mg, and 90 mg groups and the incidence of adverse events through Week 72 was also similar between the 45 mg and 90 mg groups. The system organ class (SOC) with the highest incidence of adverse events during the placebo-controlled period in either of the ustekinumab groups was “Investigations” (18.8% [6 of 32 subjects] in the placebo group, 29.7% [19 of 64 subjects] in the 45 mg group, 22.6% [14 of 62 subjects] in the 90 mg group), followed by “Infections and infestations” (18.8% [6 of 32 subjects] in the placebo group, 20.3% [13 of 64 subjects] in the 45 mg group, 24.2% [15 of 62 subjects] in the 90 mg group) and common adverse events (≥5%) in either of the ustekinumab groups were nasopharyngitis (9.4% [3 of 32 subjects] in the placebo group, 15.6% [10 of 64 subjects] in the 45 mg group, 16.1% [10 of 62 subjects] in the 90 mg group), blood triglycerides increased (3.1% [1 of 32 subjects] in the placebo group, 10.9% [7 of 64 subjects] in the 45 mg group, 0% [0 of 62 subjects] in the 90 mg group), and eosinophil count increased (3.1% [1 of 32 subjects] in the placebo group, 4.7% [3 of 64 subjects] in the 45 mg group, 6.5% [4 of 62 subjects] in the 90 mg group). The SOC with the highest incidence of adverse events through Week 72 in the combined ustekinumab group was “Infections and infestations” (68.8% [106 of 154 subjects]). No deaths were reported. The incidences of serious adverse events during the placebo-controlled period were 6.3% (2 of 32 subjects) in the placebo group, 0% (0 of 64 subjects) in the 45 mg group, and 4.8% (3 of 62 subjects) in the 90 mg group and no consistent trend was observed and serious adverse events reported by ≥2 ustekinumab-treated subjects through Week 72 were cataract (1 subject each in the 45 mg and 90 mg groups) and fall (1 subject each in the 45 mg and 90 mg groups).

In pooled 3 foreign psoriasis studies, there were no major differences in the incidence of adverse events during the placebo-controlled period through Week 12 among the placebo, 45 mg, and 90 mg groups and the incidence of adverse events during the entire reporting period was also similar between the 45 mg and 90 mg groups and between the placebo→45 mg and placebo→90 mg groups. The SOC with the highest incidence of adverse events during the placebo-controlled period was “Infections and infestations” for all groups (22.8% [167 of 732 subjects] in the placebo group, 26.3% [208 of 790 subjects] in the 45 mg group, 24.9% [197 of 792 subjects] in the 90 mg group) and common adverse

events (≥5%) in either of the ustekinumab groups were nasopharyngitis (7.9% [58 of 732 subjects] in the placebo group, 8.4% [66 of 790 subjects] in the 45 mg group, 8.0% [63 of 792 subjects] in the 90 mg group), headache (4.5% [33 of 732 subjects] in the placebo group, 5.7% [45 of 790 subjects] in the 45 mg group, 5.9% [47 of 792 subjects] in the 90 mg group), and upper respiratory tract infection (4.4% [32 of 732 subjects] in the placebo group, 5.7% [45 of 790 subjects] in the 45 mg group, 5.2% [41 of 792 subjects] in the 90 mg group). No major differences in the nature or incidence of adverse events were observed between the entire reporting period and the placebo-controlled period and the nature and incidence of adverse events were similar also between the two doses. Sudden cardiac death considered due to congestive cardiomyopathy occurred in 1 subject randomized to the 90 mg group in Study T09. The incidence of serious adverse events during the placebo-controlled period was similar among the treatment groups and the SOCs with the highest incidence of serious adverse events in either of the ustekinumab groups were "Cardiac disorders" (0% [0 of 732 subjects] in the placebo group, 0.1% [1 of 790 subjects] in the 45 mg group, 0.5% [4 of 792 subjects] in the 90 mg group) and "Infections and infestations" (0.4% [3 of 732 subjects] in the placebo group, 0% [0 of 790 subjects] in the 45 mg group, 0.5% [4 of 792 subjects] in the 90 mg group). There were no major differences either in the incidence of serious adverse events during the entire reporting period between the two doses and the SOCs with the highest incidence of serious adverse events in the combined ustekinumab group were "Cardiac disorders" (0.7% [15 of 2266 subjects]) and "Infections and infestations" (0.7% [15 of 2266 subjects]), which were the same as those during the placebo-controlled period.

**4.(ii).B.(4).2) Significant adverse events**

As shown below, the applicant explained about (a) infections, malignancy, and asthma as events theoretically associated with ustekinumab, (b) cardiovascular disorders and psoriasis as events associated with psoriasis that is the primary disease, and (c) allergy and injection site reactions as events associated with ustekinumab as an antibody preparation. PMDA's questions regarding these events and the applicant's responses are also listed below. In this section, adverse events during the entire reporting period in pooled 3 foreign psoriasis studies are based on data through Week 36 from Study T04, data through Week 52 from Study T08, and data through Week 28 from Study T09, as in the above 4.(ii).B.(4).1) Overview of safety.

**4.(ii).B.(4).2).(a) Serious infections**

Serious infections reported in Japanese Study JPN-02 were pneumonia in 1 subject in the 90 mg group during the placebo-controlled period and pharyngitis in 1 subject and cellulitis in 1 subject after Week 12 through 72. In pooled 3 foreign psoriasis studies, serious infections during the placebo-controlled period through Week 12 and during the entire reporting period were as shown in Table 32 and Table 33, respectively, and the event reported by ≥2 subjects in any group was cellulitis.

Table 32. Serious infections in 3 foreign psoriasis studies (Placebo-controlled period through Week 12)

| | Ustekinumab | | | Placebo |
|---|---|---|---|---|
| | 45 mg | 90 mg | Combined ustekinumab | |
| No. of subjects treated | 790 | 792 | 1582 | 732 |
| Mean observation period (weeks) | 12.2 | 12.1 | 12.1 | 12.0 |
| Mean treatment period (weeks) | 4.0 | 4.0 | 4.0 | 4.0 |
| No. of subjects with serious infections | 0 (0.0) | 4 (0.5) | 4 (0.3) | 3 (0.4) |
| Infections and infestations | 0 (0.0) | 4 (0.5) | 4 (0.3) | 3 (0.4) |
| Cellulitis | 0 (0.0) | 2 (0.3) | 2 (0.1) | 2 (0.3) |
| Herpes zoster disseminated | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) |
| Pneumonia | 0 (0.0) | 1 (0.1) | 1 (0.1) | 1 (0.1) |

n (%)

Table 33. Serious infections in 3 foreign psoriasis studies (Entire reporting period)

| | Ustekinumab | | | Placebo |
|---|---|---|---|---|
| | 45 mg | 90 mg | Combined ustekinumab | |
| No. of subjects treated [a] | 1110 | 1156 | 2266 | 732 |
| Total subject-years of follow-up | 725 | 742 | 1467 | 182 |
| Serious infections | 6 | 9 | 15 | 3 |
| No. of events per 100 subject-years | 0.83 | 1.21 | 1.02 | 1.65 |
| 95% CI[b] | (0.30,1.80) | (0.55, 2.30) | (0.57, 1.69) | (0.57,1.69) |

a: Placebo-to-ustekinumab crossover subjects were included in the ustekinumab group after crossover to ustekinumab.
b: Confidence interval calculated with Fisher's exact test

In Study T08, 1 subject in the 90 mg group had herpes zoster disseminated, which was a possible opportunistic infection. Although no active tuberculosis was reported in the above Japanese and foreign studies, after the data cutoff dates of these studies, 1 case of presumed reactivation of latent tuberculosis was reported in a phase III psoriasis study (Study T25), which is ongoing in Korea and Taiwan.

According to the latest foreign post-marketing safety data collected between December 31, 2008 (International Birth Date) and August 2, 2010, a total of 37 cases of serious infections were reported and based on cumulative exposure of 18,380 patient-years estimated from the latest PSUR through June 30, 2010, its frequency was considered low. There were no reports of unconventional infections or opportunistic infections etc. and 2 cases of tuberculosis and 4 cases of sepsis were reported, but the reporting rates were low, i.e. 0.01 per 100 patient-years and 0.02 per 100 patient-years, respectively.

Based on the above, although no apparent impact of ustekinumab on infections has been seen to date, as ustekinumab is a selective immunosuppressant and may increase the risk of infections or of exacerbating infections, adequate warning and precaution information will be provided on the package insert: it will be stated in the warnings section that serious infections have been reported and that ustekinumab may increase the risk of reactivation of latent tuberculosis infection, etc. Furthermore, caution statements about infections and tuberculosis will be included in the contraindications and precautions sections as well.

PMDA asked the applicant to discuss the potential for ustekinumab to increase the risk of tuberculosis infection, taking account of its possibility of affecting the expression of TNF-α, etc. and the findings from IL-12- and IL-23-related gene knockout animals, etc.

The applicant explained as follows:
Based on the results of pharmacodynamic assessments as part of foreign clinical studies in patients with psoriasis, a decrease in mRNA for TNF-α in lesional skin was observed after ustekinumab treatment, which is considered to be associated with recovery of inflammation (Study T01) and serum TNF-α levels were unchanged (Study T04). On the other hand, infection experiments suggested that IL-12- and IL-23-related gene knockout mice and mice treated with neutralizing antibodies to IL-12 and IL-23 had decreased host defense against pathogenic agents including mycobacteria and an increased susceptibility to initial mycobacterial infection in humans with IL-12- and IL-23-related gene deficiency has been reported [see "3.(iii) Summary of toxicology studies"]. However, based on clinical study data and foreign post-marketing safety data, the risk of tuberculosis associated with ustekinumab treatment is not high and it is just a potential risk under the current situation, which can be managed through selection of appropriate patients and the prevention and appropriate treatment of latent tuberculosis, in accordance with the above-mentioned draft package insert.

PMDA considers as follows:
Given that a few cases of tuberculosis have been reported in clinical studies and foreign post-marketing experience and that it has been suggested that IL-12- and IL-23-related gene knockout mice and genetically deficient humans have decreased host defense to mycobacteria, the risk of tuberculosis infection associated with ustekinumab cannot be denied and as proposed by the applicant, adequate warning and precaution information should be provided on the package insert etc. Moreover, it should also be noted that the incidence rate of tuberculosis is higher in Japan than in Europe and the US and the tuberculosis trend should be watched continuously.

Not only tuberculosis but also other serious infections are of greatest concern regarding the safety profile of ustekinumab. It is important to establish the procedures for cooperation between dermatologists who are the main physicians treating psoriasis and specialists who are capable of diagnosing and treating serious infections, in collaboration with the relevant academic societies, and take thorough measures to prevent and detect early adverse drug reactions, etc. [see "4.(ii).B.(5) Post-marketing safety measures"].

**4.(ii).B.(4).2).(b) Malignancy**
Malignancies reported in Japanese Study JPN-02 were prostate cancer in 1 subject in the 90 mg group during the placebo-controlled period and cervix carcinoma stage 0 in 1 subject after Week 12 through Week 72.

During the placebo-controlled period through Week 12 in pooled 3 foreign psoriasis studies, 2 subjects each in the placebo, 45 mg, and 90 mg groups reported malignancies and the rates of malignancies were 1.13, 0.99, and 0.98 cases per 100 subject-years of follow-up in the placebo, 45 mg, and 90 mg groups, respectively. One of the 2 subjects in the placebo group, 1 of the 2 subjects in the 45 mg group, and 2 of the 2 subjects in the 90 mg group had non-melanoma skin cancer and the rates of

non-melanoma skin cancer were 0.57, 0.49, and 0.98 cases per 100 subject-years of follow-up in the placebo, 45 mg, and 90 mg groups, respectively. During the entire reporting period, 19 subjects in the combined ustekinumab group reported malignancies and the rate of malignancies in the combined ustekinumab group was 1.30 cases per 100 subject-years of follow-up. Of the 19 subjects, 14 subjects had non-melanoma skin cancer and the rate of non-melanoma skin cancer was 0.96 cases per 100 subject-years of follow-up. Malignancies other than non-melanoma skin cancer in the remaining 5 subjects were prostate cancer (2 subjects), breast cancer (1 subject), renal cancer (1 subject), and thyroid cancer (1 subject) and no consistent trend was observed. When the number of ustekinumab-treated subjects with malignancies other than non-melanoma skin cancer during the entire reporting period (5 cases) was compared with what would be expected in the general US population according to the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) database (7.05 cases), the standardized incidence ratio (the ratio of the observed-to-expected number of cases) and its 95% confidence interval were 0.71 [0.23,1.65] and no major differences were observed. When the rate of non-melanoma skin cancer cases per 100 subject-years of follow-up was compared between clinical studies of ustekinumab vs. other biologics, as shown in Table 34, the rate in the combined ustekinumab group was similar to those with 3 other biologics.

Table 34. Comparison of the rates of non-melanoma skin cancer with ustekinumab vs. other biologics

| | Ustekinumab [a] | Infliximab [b] | Efalizumab [c] | Etanercept [d] |
|---|---|---|---|---|
| Total subject-years of follow-up [e] | 1463 | 1101 | 1784 | 1062 |
| Observed number of cases | 14 | 17 | 20 | 12 |
| No. of cases per 100 subject-years | 0.96 | 1.54 | 1.12 | 1.13 |
| 95% CI [f] | (0.52, 1.61) | (0.90, 2.47) | (0.68, 1.73) | (0.58, 1.97) |

a: Data from 3 foreign psoriasis studies
b: Data from foreign phase II and III clinical studies (Centocor's internal documents)
c: Unapproved in Japan. Data from The Dermatologic and Ophthalmic Drugs Advisory Committee, FDA [September 9, 2003, RAPTIVA™ (efalizumab)]
d: Unapproved for treatment of psoriasis in Japan. Enbrel (BLA 103795) data at the time of US approval.
e: Non-melanoma skin cancer includes basal cell carcinoma and squamous cell carcinoma.
f: Confidence interval calculated with Fisher's exact test

Eight cases of malignancies were collected from the latest foreign post-marketing safety data and except for prostate cancer reported by 3 patients, all malignancies were each reported by only 1 patient (anaplastic large cell lymphoma T- and null-cell types, breast cancer, gallbladder cancer, pancreatic carcinoma, renal cancer).

Based on the above, although no apparent impact of ustekinumab on malignancy has been seen to date, as ustekinumab is a selective immunosuppressant and may increase the risk of malignancy, the warning and precaution information concerning malignancy will be included in the warnings and precautions sections of the package insert, as in the case of other biologics.

PMDA considers as follows:
Although a causal relationship between ustekinumab and malignancy is not clear at present, as in the case of other biologics, the possibility that ustekinumab affects the host defense to malignant tumors cannot be denied and it is necessary to continue to conduct a large-scale, long-term investigation of the

relationship between ustekinumab and malignancy. Generally, psoriasis patients have previously experienced phototherapy or immunosuppressants and are particularly susceptible to non-melanoma skin cancer. Therefore, it is necessary to collect post-marketing information on the occurrence of non-melanoma skin cancer in psoriasis patients and the background of patients with non-melanoma skin cancer, etc. and investigate their relationship to ustekinumab in details.

**4.(ii).B.(4).2).(c) Asthma**

As ustekinumab inhibits Th1 cell differentiation, it is theoretically possible that ustekinumab shifts the immune response toward a Th2 phenotype and exacerbates atopic diseases. Thus, the effects of ustekinumab on asthma were investigated.

In Japanese Study JPN-02, asthma was reported by 1 subject in the 45 mg group (1.6%) and 1 subject in the 90 mg group (1.6%), but not in the placebo group. Both events were mild in severity and both subjects with asthma had prior or concurrent bronchial asthma.

In pooled 3 foreign psoriasis studies, the incidences of asthma during the placebo-controlled period through Week 12 were 0.1% (1 of 732 subjects) in the placebo group, 0% (0 of 790 subjects) in the 45 mg group, and 0.5% (4 of 792 subjects) in the 90 mg group and the incidence during the entire reporting period in the combined ustekinumab group was 0.5% (11 of 2266 subjects). No serious adverse events related to asthma were observed in ustekinumab-treated subjects and serious asthma exacerbation occurred in 1 subject in the placebo group. There were no treatment discontinuations due to asthma. While 22.5% (450 of 1996 subjects) or 1.2% (23 of 1996 subjects) of subjects enrolled in Studies T08 and T09 had prior/concurrent seasonal allergy or atopic dermatitis, respectively (this information not collected in Study T04), the incidence of seasonal allergy during the entire reporting period in the combined ustekinumab group was 0.5% (11 of 2266 subjects) and atopic dermatitis was not reported.

Based on the above, treatment with ustekinumab is unlikely to significantly affect Th2-mediated diseases such as asthma or other atopic diseases.

PMDA considers as follows:

Although there is no objection to the applicant’s view that ustekinumab has no significant effects on Th2-mediated diseases based on the currently available information, severe asthma patients were excluded from the clinical studies and there is limited clinical experience with ustekinumab in patients with concurrent atopic dermatitis etc. Thus, it is necessary to investigate the effects of ustekinumab on these diseases in more details via post-marketing surveillance and to appropriately provide the obtained information (e.g. ustekinumab has a theoretical risk of exacerbating Th2-mediated diseases) to healthcare providers in clinical settings.

**4.(ii).B.(4).2).(d) Cardiovascular disorder**

It has been reported that the risk of occlusive vascular diseases such as myocardial infarction and stroke is increased in psoriasis patients, which is considered attributable to a high prevalence, among the patients, of cardiovascular risk factors such as hypertension, hyperlipidaemia, diabetes mellitus, obesity, and smoking. Also, psoriasis itself has been reported to be a cardiovascular risk factor. Thus, as a risk to the psoriasis patient population, the impact of ustekinumab on cardiovascular adverse events was assessed.

In Japanese Study JPN-02, events classified as "cardiac disorders" or "vascular disorders" were assessed. The incidences of cardiac disorders during the placebo-controlled period were 3.1% (1 of 32 subjects, cardiac failure congestive) in the placebo group, 1.6% (1 of 64 subjects, supraventricular extrasystoles) in the 45 mg group, and 0% (0 of 62 subjects) in the 90 mg group and the incidence through Week 72 in the combined ustekinumab group was 5.8% (9 of 154 subjects, ventricular extrasystoles [5 subjects], supraventricular extrasystoles [1 subject], arrhythmia [1 subject], and left ventricular hypertrophy [1 subject], in addition to the above). The incidences of vascular disorders during the placebo-controlled period were 3.1% (1 of 32 subjects, hypertension) in the placebo group, 0% (0 of 64 subjects) in the 45 mg group, and 1.6% (1 of 62 subjects, thrombosis) in the 90 mg group and the incidence through Week 72 in the combined ustekinumab group was 5.8% (9 of 154 subjects, hypertension [7 subjects] and arteriosclerosis [1 subject], in addition to the above). The events observed in ustekinumab-treated subjects were all mild in severity.

In pooled 3 foreign psoriasis studies, the overall incidence of cardiovascular adverse events during the placebo-controlled period through Week 12 was similar for all groups, i.e. 4.5% (33 of 732 subjects) in the placebo group, 3.8% (30 of 790 subjects) in the 45 mg group, and 4.4% (35 of 792 subjects) in the 90 mg group. The overall incidences of cardiovascular adverse events during the entire reporting period were 9.2% (73 of 790 subjects) in the 45 mg group, 9.8% (78 of 792 subjects) in the 90 mg group, 6.3% (20 of 320 subjects) in the placebo→45 mg group, and 3.3% (12 of 364 subjects) in the placebo→90 mg group, and there was no increase in incidence with increasing dose.

As serious cardiovascular adverse events, objective events of "serious myocardial infarction", "serious stroke", and "cardiovascular death" were identified and assessed. As a result, 5 serious cardiovascular adverse events occurred in ustekinumab-treated subjects only during the placebo-controlled period (2 events in the 45 mg group, 3 events in the 90 mg group) and the rates were 0 events per 100 subject-years in the placebo group, 0.98 events per 100 subject-years in the 45 mg group, and 1.47 events per 100 subject-years in the 90 mg group. The rates during the entire reporting period were 0.55 events per 100 subject-years in the placebo group (since myocardial infarction [1 subject] occurred during the follow-up period after study drug discontinuation, this event was analyzed as occurring during the entire reporting period, instead of during the placebo-controlled period) and 0.61 events per 100 subject-years in the combined ustekinumab group. When "serious ischaemic events" were assessed as serious cardiovascular adverse events, the rates during the placebo-controlled period were

0 events per 100 subject-years in the placebo group, 1.48 events per 100 subject-years in the 45 mg group, and 1.47 events per 100 subject-years in the 90 mg group and the rates during the entire reporting period were 0.55 events per 100 subject-years in the placebo group and 0.95 events per 100 subject-years in the combined ustekinumab group.

Based on the above, it was considered that there was no apparent trend of increased cardiovascular risk associated with ustekinumab.

PMDA asked the applicant to explain their view on the appropriateness of the use of ustekinumab in psoriasis patients with severe cardiovascular disease.

The applicant explained as follows:
Although patients with stable cardiovascular disease were not excluded from Foreign Studies T08 and T09 and 5.6% of the subjects had myocardial infarction, coronary artery bypass, stroke, transient ischaemic attack, or atherosclerotic cardiovascular disease at baseline, as these clinical studies showed no apparent trend of increased cardiovascular risk associated with ustekinumab, there should be no problem with the use of ustekinumab even in patients with concurrent severe cardiovascular disease as long as they are appropriately managed by physicians and their symptoms are stable.

PMDA considers as follows:
Since there are no findings suggestive of increased cardiovascular risk in IL-12- and IL-23-related gene knockout animals and genetically deficient humans, at present, there is no need to restrict the use of ustekinumab in patients with cardiovascular disease including those with severe disease. However, as there is limited clinical experience with ustekinumab in these patients in the clinical studies, it is necessary to continue to carefully investigate the effects of ustekinumab on the cardiovascular system via post-marketing surveillance etc.

**4.(ii).B.(4).2).(e) Psoriasis**
In order to assess the effects of ustekinumab on psoriasis rebound, psoriasis-related adverse events and psoriasis rebound after stopping therapy were investigated.

In Japanese Study JPN-02, the incidences of psoriasis-related adverse events during the placebo-controlled period were 25.0% (8 of 32 subjects) in the placebo group, 1.6% (1 of 64 subjects) in the 45 mg group, and 4.8% (3 of 62 subjects) in the 90 mg group, and the incidence was lower in ustekinumab-treated subjects compared to placebo-treated subjects. The incidence through Week 72 in the combined ustekinumab group was 5.2% (8 of 154 subjects).

In pooled 3 foreign psoriasis studies, the incidences of psoriasis-related adverse events during the placebo-controlled period through Week 12 were 2.3% (17 of 732 subjects) in the placebo group, 0.4% (3 of 790 subjects) in the 45 mg group, and 1.4% (11 of 792 subjects) in the 90 mg group, and

the incidence was lower in ustekinumab-treated subjects compared to placebo-treated subjects. The incidence during the entire reporting period in the combined ustekinumab group was 1.2% (27 of 2266 subjects).

Psoriasis rebound was evaluated in Studies T04 and T08 where evaluation was continued also after stopping ustekinumab therapy. Rebound was defined as the occurrence of new erythrodermic or pustular psoriasis or exacerbation of psoriasis to ≥125% of the baseline PASI within 3 months after the last dose of ustekinumab. In Study T04, 2 subjects had PASI ≥125% of baseline. In Study T08, the criteria for rebound were not fulfilled between the last dose and Week 40 for any subject in the treatment withdrawal group.

Based on the above, no important findings were observed regarding the effects of ustekinumab on psoriasis-related events and psoriasis rebound after stopping therapy.

As exacerbation and new onset of psoriasis have been reported with anti-TNF agents and a relevant precautionary statement is included in the package insert, PMDA asked the applicant to present the occurrence of psoriasis in non-psoriasis clinical studies of ustekinumab and then explain whether a similar precautionary statement is necessary also for ustekinumab.

The applicant explained as follows:
In addition to psoriasis clinical studies, multiple sclerosis and Crohn's disease clinical studies were conducted overseas and a total of 336 subjects received ustekinumab. In these clinical studies, serious psoriasis was not reported and non-serious psoriasis was reported by 1 patient with Crohn's disease, but the patient had a history of psoriasis and its causal relationship to ustekinumab was denied. As described above, Japanese and foreign clinical studies showed no relationship between ustekinumab and exacerbation or new onset of psoriasis and although the mechanism of exacerbation or new onset of psoriasis induced by anti-TNF agents has not been elucidated at molecular level, the molecular target of ustekinumab is different from that of anti-TNF agents. Therefore, this risk may be lower with ustekinumab compared with anti-TNF agents and a precautionary statement in the package insert etc. should be unnecessary at present.

PMDA accepts the applicant's response at present, but considers that it is necessary to collect further information on the effects of ustekinumab in patients with other diseases, etc. and continue to investigate the risk associated with ustekinumab because the clinical studies of ustekinumab were conducted primarily in psoriasis patients and it is difficult to appropriately assess exacerbation or new onset of psoriasis in psoriasis patients.

**4.(ii).B.(4).2).(f) Injection site reactions and allergic reactions**

In Japanese Study JPN-02, the incidences of injection site reactions were 0.6% (1 of 158 subjects) following administration of placebo and 1.9% (3 of 154 subjects) following administration of

ustekinumab and these events were all mild in severity. While no cases of anaphylactic reactions or serum sickness reactions were reported, as adverse events of suspected allergic reactions, eczema (7.1% [11 of 154 subjects]), urticaria (3.9% [6 of 154 subjects]), pruritus (1.9% [3 of 154 subjects]), injection site urticaria (0.6% [1 of 154 subjects]), rash (0.6% [1 of 154 subjects]), and pruritus generalised (0.6% [1 of 154 subjects]) were observed. The incidence of anti-ustekinumab antibody development in the combined ustekinumab group was 6.5% and none of the antibody-positive subjects had an adverse event of suspected anaphylactic reaction and the 3 subjects with injection site reactions were not antibody-positive.

In pooled 3 foreign psoriasis studies, the incidences of injection site reactions were 2.6% (60 of 2304 subjects) following administration of placebo and 3.1% (71 of 2266 subjects) following administration of ustekinumab and no major differences were observed. Although no adverse events of suspected anaphylactic reactions or serum sickness-like reactions were observed, as adverse events of suspected allergic reactions, rash and urticaria were reported and the incidence was <1% for both events. The incidence of anti-ustekinumab antibody development in the combined ustekinumab group was 3.7% and none of the antibody-positive subjects had an adverse event of suspected anaphylactic reaction. In foreign phase III studies (Studies T08 and T09), the incidences of injection site reactions were 7.0% (5 of 71 subjects) in antibody-positive subjects and 3.8% (71 of 1870 subjects) in antibody-negative subjects, which indicated that there is no relationship between anti-ustekinumab antibody development and injection site reactions.

Based on the latest foreign post-marketing safety data, 1 case of anaphylactic reaction and 4 cases of hypersensitivity were collected and as it was considered that serious allergic reactions should be recognized as a risk associated with ustekinumab, it will be stated, as precaution information, in the adverse reactions section of the package insert that serious allergic reactions such as possible anaphylactic events and angioedema may occur.

PMDA considers as follows:
The precaution information concerning serious allergic reactions associated with ustekinumab is appropriate at present. Meanwhile, as it seems that the occurrence of serious allergic reactions tends to increase in the foreign post-marketing experience compared to in the clinical studies, it is necessary to continue to watch the trend of occurrence and review the precaution information as appropriate. During treatment with ustekinumab, it is important to be prepared so that drug therapy and emergency measures can be used promptly in response to anaphylaxis etc. and then to closely monitor the patient's condition.

In addition, the occurrence of autoimmune disease, demyelinating disease, interstitial pneumonia, blood disorder, and hepatic disorder etc., which are considered to be important adverse reactions to anti-TNF agents (similar drugs), was also investigated based on the clinical study data and the latest foreign post-marketing safety data etc., which has suggested no risk of these adverse events associated

with ustekinumab at present. Thus, no particular precaution information etc. are necessary. However, given that the clinical experience with ustekinumab is very limited compared to the experience with anti-TNF agents, that the mechanism of these adverse events associated with anti-TNF agents is not elucidated, and that anti-TNF agents and ustekinumab are both antibody products affecting the immune system, etc., the possibility that ustekinumab also causes similar adverse reactions cannot be denied. Therefore, it is necessary to carefully investigate the occurrence of these events also via post-marketing surveillance.

**4.(ii).B.(5) Post-marketing safety measures**

PMDA considers as follows:

Since the possibility that ustekinumab causes adverse reactions such as serious infections and malignancy cannot be denied and the long-term safety of ustekinumab is unknown in many aspects, as in the case of existing biologics, a large-scale drug use-results survey with the physicians and all the patients registered and a long-term special drug use-results survey to appropriately follow the patients for the development of malignancy, etc., should be conducted. In order to promote proper use of ustekinumab, information should be provided to healthcare providers and patients appropriately and promptly by giving detailed materials to healthcare providers such as physicians, developing a patient's guide etc., which describe the risks and benefits of ustekinumab in an appropriate and easy-to-understand manner, and collecting and disclosing post-marketing information accordingly via the Internet, etc.

Furthermore, dermatologists are the main physicians to treat psoriasis, and it is essential for them, prior to the use of ustekinumab, to establish cooperation with internists, etc., who are capable of handling serious adverse drug reactions such as infections, in terms of safety measures. Thus, PMDA asked the applicant to explain in details about the requirements for medical institutions to use ustekinumab and the specific way of cooperation with internists, etc.

The applicant explained as follows:

The requirements for medical institutions to use ustekinumab are as follows: Ustekinumab can be used under the management/supervision/guidance of specialist(s) who are familiar with the diagnosis and treatment of psoriasis and who know the risks of ustekinumab very well; and tuberculosis screening can be performed and adverse drug reactions including serious infections can be diagnosed and treated at the medical institution or in its affiliated medical institution. The requirements for affiliated medical institutions are as follows: tuberculosis screening can be performed and adverse drug reactions including serious infections can be diagnosed and treated in cooperation with the prescribing medical institution (except for general hospitals having relevant cooperating departments). Moreover, the procedures for cooperation between the medical institutions have been planned as follows: (a) Affiliated medical institutions and cooperating physicians there will be identified through contacts with physicians using ustekinumab and not only prescribing physicians but also cooperating physicians will be explained about the safety profile of ustekinumab and actions to be taken in the

event of adverse drug reactions and the importance of determining whether or not to use ustekinumab, etc., (b) prescribing physicians will be requested to instruct their patients to contact them promptly if any abnormality occurs after administration of ustekinumab and to refer their patients to the affiliated medical institutions promptly if adverse drug reactions such as infections are suspected, and (c) portable patient cards for the patients to visit the affiliated medical institutions with and forms (patient diaries, etc.) that can be shared between the prescribing physicians and the affiliated medical institutions and that are used by patients themselves to record their health status will be prepared, etc.

As cooperation from the relevant academic societies, etc., is also considered essential for promoting proper use of ustekinumab and implementing safety measures, the Japanese Dermatological Association will be requested to take the initiative in developing a guideline for the use of ustekinumab.

PMDA considers as follows:
The applicant's response is largely acceptable, but it is important to confirm that cooperation with other departments/other medical institutions is ensured, via post-marketing surveillance.

## III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

### 1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

### 2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the documents appended to the new drug application (5.3.3.2.1, 5.3.5.1.2-1). As a result, enrollment of subjects who met the exclusion criteria of the protocol and flaws in the contract for the partial transfer of trial-related duties were found at some trial sites, but PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

## IV. Overall Evaluation

Based on the submitted data, the efficacy of ustekinumab in the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy has been demonstrated and its safety is acceptable in view of its observed benefits. Since ustekinumab is a

biologic with a novel mechanism of action and offers a new therapeutic option, it has clinical significance. The INDICATION statement and the DOSAGE AND ADMINISTRATION statement need to be further discussed. Regarding safety, serious adverse drug reactions such as infections may occur following administration of ustekinumab. Therefore, prior to the use of ustekinumab, the patient's symptoms, etc. should be monitored closely and the risks and benefits of ustekinumab should be weighed. A post-marketing drug use-results survey, which covers all the patients treated with ustekinumab, should be conducted to further investigate the safety of ustekinumab in psoriasis patients.

The application may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

**Review Report (2)**

November 10, 2010

**I. Product Submitted for Registration**

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010

**II. Content of the Review**

The outlines of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, 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) Indications**

PMDA concluded that ustekinumab should be indicated only for the patients who have had an inadequate response or intolerance to phototherapy or conventional systemic therapy, which was supported by the expert advisors. PMDA considered that the INDICATION statement should be modified to include the following statements in the Precautions for Indications section of the package insert: ustekinumab should be used in (a) patients who have a body surface area involvement of ≥10% and who have had an inadequate response to conventional systemic therapy including UV-light therapy (excluding biologics) or (b) patients with refractory skin lesion or joint inflammation. PMDA requested the applicant to modify the indications and the applicant accepted it.

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

In addition, PMDA instructed the applicant to include in the package the statement to the effect that ustekinumab should only be used by physicians who are familiar with the treatment of psoriasis, etc. to ensure correct diagnosis, selection of eligible patients, and the proper use of ustekinumab, and that ustekinumab should be used in cooperation with internists, etc., who are capable of handling adverse reactions to ustekinumab. The applicant responded that in order to give adequate warning, it will be stated in the WARNING section of the package insert that ustekinumab should be used by physicians

with experience in treating psoriasis in cooperation with physicians with adequate knowledge about ustekinumab.

**(2) Dosage and administration**

PMDA has concluded that a dose increase should be recommended as follows: "If the effect is insufficient, a dose of 90 mg may be used", which was supported by the expert advisors. PMDA considered that the DOSAGE AND ADMINISTRATION statement should be modified as shown below and that it should be stated in the Precautions of Dosage and Administration section that treatment with ustekinumab should not be continued without careful consideration if the patient does not respond to an increased dose of ustekinumab. PMDA requested the applicant to take actions accordingly and the applicant accepted it.

[Dosage and administration]
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.

Since ustekinumab is administered every 12 weeks after Week 4, it is not a heavy burden for most patients to receive injections at the medical institution. Therefore, patient self-administration has not been proposed.

**(3) Post-marketing surveillance etc.**

PMDA has concluded as follows

Ustekinumab may cause adverse reactions including serious infections. When ustekinumab is indicated for treatment of psoriasis, it is necessary to ensure the patient's safety with close cooperation between dermatologists and internists etc. Thus, after the market launch, a drug use-results survey, which covers all the patients treated with ustekinumab, should be conducted until data from a certain number of patient will be accumulated, in order to obtain safety information on ustekinumab in psoriasis patients as soon as possible and confirm the effectiveness of safety measures taken in cooperation with other departments/other medical institutions. Furthermore, a long-term, specified drug use-results survey to monitor the development of infections and malignancy should be conducted. On the basis of the above conclusion, PMDA requested the applicant to take actions accordingly.

The applicant responded as follows:

A long-term, specified drug use-results survey with an observation period of 52 weeks, which covers all the patients treated with ustekinumab, will be conducted. For this survey, (a) the priority items will be allergy, cardiac disorder, autoimmune disease, pancytopenia, interstitial pneumonia, demyelinating disease, and hepatic disorder, etc., which have been reported with anti-TNF agents, as well as infections, tuberculosis, and malignancy, (b) the following information will be collected: the efficacy and safety of an increased dose of ustekinumab, the safety of switching from other biologics to

ustekinumab, the actual state of concomitant use with phototherapy or other systemic therapies, the effects of ustekinumab on atopic diseases such as asthma and the cardiovascular system, etc., the efficacy of ustekinumab in patients with diabetes co-morbidity, and disease activity as measured by DAS 28 in patients with psoriatic arthritis, etc. and (c) analyses will be performed when the information from 1500 patients have been collected, but the survey will be continued until the regulatory authority's final evaluation is obtained. Patients will be followed for the development of serious infections and malignancy for up to 3 years.

PMDA considers that the survey should be conducted promptly and the obtained results should be provided to clinical practice appropriately.

**III. Overall Evaluation**

As a result of the above review, PMDA concludes that ustekinumab may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

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

[Dosage and administration]
The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) is 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.

[Conditions for approval]
The applicant is required to:
(1) Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of Ustekinumab.
(2) Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the long-term safety of the product and the occurrence of infections etc.